

12/01/97
JC529 U.S. PTO

Assistant Commissioner of Patents
Washington, D. C. 20231

Sir:

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of:

Inventor(s): Thomas J. Kipps, Sanjai Sharma, Mark Cantwell

For: **NOVEL EXPRESSION VECTORS CONTAINING ACCESSORY MOLECULE LIGAND GENES AND THEIR USE FOR IMMUNOMODULATION AND TREATMENT OF MALIGNANCIES AND AUTOIMMUNE DISEASE**

Enclosed are:

- X 110 page(s) specification; 8 page(s) claims;
1 page(s) abstract.
- X 30 sheets of drawings (X informal formal)
- X Declaration and Power of Attorney (signed X unsigned)
- Assignment of the invention to: _____
- Certified copy(s) of priority documents ()
- X A Verified Statement Claiming Small Entity Status under 37 CFR §1.9 and §1.27.
- X Sequence Listing and Statement and Sequence Listing.
- Preliminary Amendment

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

TB608349181US
Express Mail mailing no.

December 1, 1997
date of deposit

Jeanette M. Olivera

name of person mailing paper

Jeanette M. Olivera

signature of person mailing paper

The filing fee has been calculated as shown below:

-Statutory Basic Filing Fee		(\$790)	\$ 790.00
-Total Claims	<u>83</u>	(-20 <u>63</u> x \$22)	\$1,386.00
-Independent Claims	<u>17</u>	(-3 <u>14</u> x \$82)	\$1,148.00
-Multiple Dependent Claim(s)		(\$270)	\$ 270.00
-Surcharge 37 CFR 1.16(e)		(\$130)	\$ 0.00
		TOTAL OF ABOVE CALCULATIONS	\$3,594.00
		Reduction for Small Entity (%)	\$1,797.00
		Assignment (\$40)	\$ 0.00
		TOTAL FEES SUBMITTED HEREWITH	\$1,797.00

This application is filed without fee or signed declaration pursuant to 37 CFR §1.53.

- X A check in the amount of \$1,797.00 to cover the above fees is enclosed.
- X The Commissioner is hereby authorized to charge payment of the fees associated with this communication, or credit any overpayment, to Deposit Account 12-2475. A duplicate copy of this sheet is enclosed.

Respectfully Submitted

LYON & LYON

Dated: 12/1/97

Jeff Guise
Jeffrey W. Guise
Reg. No. 34,613

First Interstate World Center
633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
(619) 552-8400
(213) 955-0440 (Fax)

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **NOVEL EXPRESSION VECTORS CONTAINING ACCESSORY MOLECULE LIGAND GENES AND THEIR USE FOR IMMUNOMODULATION AND TREATMENT OF MALIGNANCIES AND AUTOIMMUNE DISEASE** the specification of which

X _____ is attached hereto.

_____ was filed on _____ as Application Serial No. _____ and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
_____	_____	_____	Yes	No
_____	_____	_____	Yes	No

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Jeffrey W. Guise, Reg. No. 34,613.

Kindly recognize as associate attorney: _____ and the following:

Roland N. Smoot, Reg. No. 18,718; Conrad R. Solum, Jr. Reg. No. 20,467; James W. Geriak, Reg. No. 20,233; Robert M. Taylor, Jr., Reg. No. 19,848; Samuel B. Stone, Reg. No. 19,297; Douglas E. Olson, Reg. No. 22,798; Robert E. Lyon, Reg. No. 24,171; Robert C. Weiss, Reg. No. 24,939; William E. Thomson, Jr., Reg. No. 29,719; Richard E. Lyon, Jr., Reg. No. 26,300; John D. McConaghy, Reg. No. 26,773; William C. Steffin, Reg. No. 26,811; Coe A. Bloomberg, Reg. No. 26,605; J. Donald McCarthy, Reg. No. 25,119; John M. Benassi, Reg. No. 27,483; James H. Shalek, Reg. No. 29,749; Allan W. Jansen, Reg. No. 29,395; Robert W. Dickerson, Reg. No. 29,914; Roy L. Anderson, Reg. No. 30,240; David B. Murphy, Reg. No. 31,125; James C. Brooks, Reg. No. 29,898; Jeffrey M. Olson, Reg. No. 30,790; Steven D. Hemminger, Reg. No. 30,755; Jerrold B. Reilly, Reg. No. 32,293; Paul H. Meier, Reg. No. 32,274; John A. Rafter, Jr., Reg. No. 31,653; Kenneth H. Ohriner, Reg. No. 31,646; Mary S. Consalvi, Reg. No. 32,212; Bradford J. Duft, Reg. No. 32,219; Suzanne L. Biggs, Reg. No. 30,158; F.T. Alexandra Mahaney, Reg. No. 37,668; Jeffrey W. Guise, Reg. No. 34,613; Sheldon O. Heber, Reg. No. 38,179; Anthony C. Chen, Reg. No. 38,673; Charles S. Berkman, Reg. No. 38,077, Gary H. Silverstein, Reg. No. 39,372 and Sheryl R. Silverstein, Reg. No. P-40,812 of LYON & LYON, 633 West Fifth Street, Suite 4700, Los Angeles, California 90071-2066 telephone (619) 552-8400.

Address all telephone calls to Jeffrey W. Guise at telephone no. (619) 552-8400.

Address all correspondence to Jeffrey W. Guise, Esq., LYON & LYON, 633 West Fifth Street, Suite 4700, Los Angeles, CA 90071-2066.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Full name of sole or first inventor Thomas J. Kipps

Inventor's signature _____ Date: _____

Residence 731 Fresca Court, Solana Beach, CA 92075 Citizenship United States

Post Office Address Same as above

Full name of second inventor Sanjai Sharma

Inventor's signature _____ Date: _____

Residence 11478 Duenda Road, San Diego, CA 92127 Citizenship India

Post Office Address Same as above

Full name of third inventor Mark Cantwell

Inventor's signature _____ Date: _____

Residence 7015 Charmant Drive, #243, San Diego, CA 92122 Citizenship United States

Post Office Address Same as above

Applicant or Patentee: Kipps et al.
Serial or Patent No.: Unassigned
Filed or Issued: Filed Herewith
For: NOVEL EXPRESSION VECTORS CONTAINING ACCESSORY MOLECULE LIGAND GENES AND THEIR USE FOR IMMUNOMODULATION AND TREATMENT OF MALIGNANCIES AND AUTOIMMUNE DISEASE

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(e) and 1.27(d)) - NONPROFIT ORGANIZATION**

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION: UNIVERSITY OF CALIFORNIA
ADDRESS OF ORGANIZATION: Technology Transfer Office
9500 Gilman Drive
La Jolla, CA 92093

TYPE OF ORGANIZATION:

- [X] UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
[] TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3))
[] NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
(NAME OF STATE:)
(CITATION OF STATUTE:)
[] WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA
[] WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
(NAME OF STATE:)
(CITATION OF STATUTE:)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, with regard to the invention entitled NOVEL EXPRESSION VECTORS CONTAINING ACCESSORY MOLECULE LIGAND GENES AND THEIR USE FOR IMMUNOMODULATION AND TREATMENT OF MALIGNANCIES AND AUTOIMMUNE DISEASE by inventor(s) Kipps et al. described in

- [X] the specification filed herewith.
[] application serial no. _____, filed _____.
[] patent no. _____, issued _____.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____

ADDRESS _____

[] INDIVIDUAL [] SMALL BUSINESS CONCERN [] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Martin Rachmeler
TITLE OF PERSON IN ORGANIZATION: Director
ADDRESS OF PERSON SIGNING: 9500 Gilman Drive, La Jolla, CA 92093-0093

Signature



Date

12/1/97

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:) Group Art Unit:
Thomas J. Kipps et al.)
Serial No. To Be Assigned) Examiner:
Filed: Herewith)
For: NOVEL EXPRESSION VECTORS)
CONTAINING ACCESSORY)
MOLECULE LIGAND GENES AND)
THEIR USE FOR IMMUNO-)
MODULATION AND TREATMENT OF)
MALIGNANCIES)

STATEMENT UNDER 37 C.F.R. § 1.821 (F)

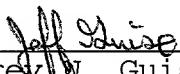
Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I hereby state that the content of the paper and computer readable copies of the Sequence Listing, submitted in accordance with 37 C.F.R. § 1.821 (e), (f) and (g), or § 1.825 (d) and (b) respectively, are the same.

Respectfully submitted,

LYON & LYON LLP


Jeffrey W. Guise
Registration No. 34,613

633 West Fifth Street
Suite 4700
Los Angeles, California 90071
(619) 552-8400

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

TB608349181US

Express Mail mailing no.

December 1, 1997

date of deposit

Jeanette M. Olivera

name of person mailing paper

Jeanette M. Olivera

signature of person mailing paper

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANTS: Kipps, Thomas J.
Sharma, Sanjai
Cantwell, Mark
- (ii) TITLE OF INVENTION: NOVEL EXPRESSION VECTORS
CONTAINING ACCESSORY
MOLECULE LIGAND GENES AND
THEIR USE FOR IMMUNO-
MODULATION AND TREATMENT OF
MALIGNANCIES
- (iii) NUMBER OF SEQUENCES: 44
- (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Lyon & Lyon
(B) STREET: 633 West Fifth Street
Suite 4700
(C) CITY: Los Angeles
(D) STATE: California
(E) COUNTRY: U.S.A.
(F) ZIP: 90071-2066
- (v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5" Diskette,
1.44 Mb storage
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: IBM P.C. DOS 5.0
(D) SOFTWARE: FastSeq Version 2.0
- (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: To Be Assigned
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 60/132145
(B) FILING DATE: 12/9/96

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Guise, Jeffrey W.
(B) REGISTRATION NUMBER: 34,613
(C) REFERENCE/DOCKET NUMBER: 231/003

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (213) 489-1600
(B) TELEFAX: (213) 955-0440
(C) TELEX: 67-3510

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 786 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

ATGATCGAAA	CATAACAACCA	AACTTCTCCC	CGATCTGCGG	CCACTGGACT	GCCCATCAGC	60
ATGAAAATT	TTATGTATT	TCTTACTGTT	TTTCCTTATCA	CCCAGATGAT	TGGGTCA	120
CTTTTGCTG	TGTATCTTCA	TAGAAGGTTG	GACAAGATAG	AAGATGAAAG	GAATCTTCAT	180
GAAGATTTG	TATTCATGAA	AACGATACAG	AGATGCAACA	CAGGAGAAAG	ATCCTTATCC	240
TTACTGA	ACT GTGAGGAGAT	TAAAAGCCAG	TTTGAAGGCT	TTGTGAAGGA	TATAATGTTA	300
ACAAAGAGG	AGACGAAGAA	AGAAAACAGC	TTTGAAATGC	AAAAAGGTGA	TCAGAAC	360
CAAATTGCGG	CACATGTCAT	AAAGTGAGGCC	AGCAGTAAAA	CAACATCTGT	GTTACAGTGG	420
GCTAAAAAG	GATACTACAC	CATGAGCAAC	AACTTGGTAA	CCCTGGAAAA	TGGGAAACAG	480
CTGACCGTTA	AAAGACAAGG	ACTCTATTAT	ATCTATGCC	AAGTCACCTT	CTGTTCCAAT	540
CGGGAAAGCTT	CGAGTCAAGC	TCCATTATA	GCCAGCCTCT	GCCTAAAGTC	CCCCGGTAGA	600
TTCGAGAGAA	TCTTACTCAG	AGCTGCAAAT	ACCCACAGTT	CCGCCAAACC	TTGCGGGCAA	660
CAATCCATT	TC	ACTTGGGAGG	AGTATTGAA	TTGCAACCAG	GTGCTTCGGT	720
GTGACTGATC	CAAGCCAAGT	GAGCCATGGC	ACTGGCTTC	CGTCCTTGG	CTTACTCAAA	780
CTCTGA						786

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 783 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

ATGATAGAAA	CATAACGCCA	AACTTCCCCC	AGATCCGTGG	CAACTGGACT	TCCAGCGAGC	60		
ATGAAGATT	TTATGTATTT	ACTTA	CTGTGTT	TTCCCTTATCA	CCC	AAATGAT	TGGATCTGTG	120
CTTTTGCTG	TGTATCTCA	TAGAAGATTG	GATAAGGTG	AAGAGGAAGT	AAAC	CTTCAT	180	
GAAGATTTG	TATT	CATAAAA	AAAGCTAAAG	AGATGCAACA	AAGGAGAAGG	ATCTT	TATCC	240
TTGCTGA	ACT	GTGAGGAGAT	GAGAAGGC	AA	TTGTC	AAAGGAGAAGG	TATAACGT	300
AACAAAGAAG	AGAAAAAAGA	AAACAGCTT	GAAATGCAA	GAGGTGATGA	GGATC	CCTCAA	360	
ATTGCAGCAC	ACGTTGTAAG	CGAAGCCAAC	AGTAATGCAG	CATCCGTTCT	ACAGT	GGGCC	420	
AAGAAAGGAT	ATTATACCAT	GAAAAGCAAC	TTGGTAATGC	TTGAAAATGG	GAAAC	AGCTG	480	
ACGGTTAAA	GAGAAGGACT	CTATTATGTC	TACACTCAAG	TCACCTCTG	CTCTA	ATCGG	540	
GAGCCTTCGA	GTCAACGCC	ATT	CATCGTC	GGCCTCTGGC	TGAAG	CCAG	600	
GAGAGAATCT	TACTCAAGGC	GGCAAATACC	CACAGTTCC	CCCAGCTT	CGAGC	AGCAG	660	
TCTGTTCACT	TGGCGGGAGT	GTTTGAATT	CAAGCTGGTG	CTTCTGTGTT	TGTCAACGT	720		
ACTGAAGCAA	GCCAAGTGAT	CCACAGAGTT	GGCTTCTCAT	CTTTGGCTT	ACTCAA	ACTC	780	
TGA							783	

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 783 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

ATGATCGAAA	CATAAACCCA	AACTTCTCCC	CGATCTGCGG	CCACTGGACT	GCCC	CATCAGC	60	
ATGAAAATT	TTATGTATTT	ACTTA	CTGTGTT	TTT	CCAGATGAT	TGGGT	CAGCA	120
CTTTTGCTG	TGTATCTCA	TAGAAGATTG	GATAAGGTG	AAGAGGAAGT	AAAC	CTTCAT	180	
GAAGATTTG	TATT	CATAAAA	AAAGCTAAAG	AGATGCAACA	AAGGAGAAGG	ATCTT	TATCC	240
TTGCTGA	ACT	GTGAGGAGAT	GAGAAGGC	AA	TTGTC	AAAGGAGAAGG	TATAACGT	300
AACAAAGAAG	AGAAAAAAGA	AAACAGCTT	GAAATGCAA	GAGGTGATGA	GGATC	CCTCAA	360	
ATTGCAGCAC	ACGTTGTAAG	CGAAGCCAAC	AGTAATGCAG	CATCCGTTCT	ACAGT	GGGCC	420	
AAGAAAGGAT	ATTATACCAT	GAAAAGCAAC	TTGGTAATGC	TTGAAAATGG	GAAAC	AGCTG	480	
ACGGTTAAA	GAGAAGGACT	CTATTATGTC	TACACTCAAG	TCACCTCTG	CTCTA	ATCGG	540	
GAGCCTTCGA	GTCAACGCC	ATT	CATCGTC	GGCCTCTGGC	TGAAG	CCAG	600	
GAGAGAATCT	TACTCAAGGC	GGCAAATACC	CACAGTTCC	CCCAGCTT	CGAGC	AGCAG	660	
TCTGTTCACT	TGGCGGGAGT	GTTTGAATT	CAAGCTGGTG	CTTCTGTGTT	TGTCAACGT	720		
ACTGAAGCAA	GCCAAGTGAT	CCACAGAGTT	GGCTTCTCAT	CTTTGGCTT	ACTCAA	ACTC	780	
TGA							783	

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 786 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

ATGATCGAAA	CATAAACCCA	AACTTCTCCC	CGATCTGCGG	CCACTGGACT	GCCC	CATCAGC	60
------------	------------	------------	------------	------------	------	---------	----

ATGAAAATTT TTATGTATTT ACTTACTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG 120
 CTTTTGCTG TGTATCTTCA TAGAAGGTG GACAAGATAG AAGATGAAAG GAATCTTCAT 180
 GAAGATTTG TATTCAATGAA AACGATACAG AGATGCAACA CAGGAGAAAG ATCCTTATCC 240
 TTACTGAACT GTGAGGGAGAT TAAAAGCCAG TTTGAAGGCT TTGTGAAGGA TATAATGTTA 300
 AACAAAGAGG AGACGAAGAA AGAAAACAGC TTTGAAATGC AAAAAGGTGA TCAGAACATCCT 360
 CAAATTGCGG CACATGTCAT AAGTGAGGCC AGCAGTAAAA CAACATCTGT GTTACAGTGG 420
 GCTGAAAAAG GATACTACAC CATGAGCAAC AACTTGGTAA CCCTGGAAAA TGGGAAACAG 480
 CTGACCGTTA AAAGACAAGG ACTCTATTAT ATCTATGCC AAGTCACCTT CTGTTCCAAT 540
 CGGGAAAGCTT CGAGTCAAAGC TCCATTATA GCCAGCCTCT GCCTAAAGTC CCCCGTAGA 600
 TTCGAGAGAA TCTTACTCAG AGCTGCAAAT ACCCACAGTT CCGCCAAACC TTGCGGGCAA 660
 CAATCCATTCACTTGGGAGG AGTATTGAA TTGCAACCAG GTGCTTCGGT GTTTGTCAAT 720
 GTGACTGATC CAAGCCAAGT GAGCCATGGC ACTGGCTTCA CGTCCTTTGG CTTACTCAAA 780
 CTCTGA 786

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 783 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

ATGATCGAAA CATAACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC 60
 ATGAAAATTT TTATGTATTT ACTTACTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG 120
 CTTTTGCTG TGTATCTTCA TAGAAGATTG GATAAGGTCG AAGAGGAAGT AAACCTTCAT 180
 GAAGATTTG TATTCAATAAA AAAGCTAAAG AGATGCAACA AAGGAGAAAGG ATCCTTATCC 240
 TTGCTGAACT GTGAGGGAGAT GAGAAGGCAA TTTGAAGACC TTGTCAAGGA TATAACGTTA 300
 AACAAAGAAG AGAAAAAAAGA AAACAGCTT GAAATGCAAA GAGGTGATGAA GGATCCTCAA 360
 ATTGCAAGCAC ACGTTGTAAG CGAAGCCAAAC AGTAATGCAG CATCCGTCT ACAGTGGGCC 420
 AAGAAAGGAT ATTATACCAT GAAAAGCAAC TTGGTAATGC TTGAAATGG GAAACAGCTG 480
 ACGGTTAAA GAGAAGGACT CTATTATGTC TACACTCAAG TCACCTCTG CTCTAACCGG 540
 GAGCCTTCGA GTCAACGCC ATTCACTGTC GGCCCTCTGGC TGAAGCCAG CATTGGATCT 600
 GAGAGAATCT TACTCAAGGC GGCAAATACC CACAGTTCT CCCAGCTTTG CGAGCAGCAG 660
 TCTGTTCACT TGGCGGGAGT GTTTGAATTAA CAAGCTGGTG CTTCTGTGTT TGTCAACGTT 720
 ACTGAAGCAA GCCAAGTGAT CCACAGAGTT GGCTCTCAT CTTTTGGCTT ACTCAAACTC 780
 TGA 783

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 786 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

ATGATAGAAA CATACACGCCA ACCTTCCCCC AGATCCGTGG CAACTGGACT TCCAGCGAGC 60
 ATGAAGATTT TTATGTATTT ACTTACTGTT TTTCTTATCA CCCAGATGAT TGGGTCAGCA 120
 CTTTTGCTG TGTATCTTCA TAGAAGGTG GACAAGATAG AAGATGAAAG GAATCTTCAT 180
 GAAGATTTG TATTCAATGAA AACGATACAG AGATGCAACA CAGGAGAAAG ATCCTTATCC 240
 TTACTGAACT GTGAGGGAGAT TAAAAGCCAG TTTGAAGGCT TTGTGAAGGA TATAATGTTA 300

AACAAAGAGG	AGACGAAGAA	AGAAAACAGC	TTTGAAATGC	AAAAAGGTGA	TCAGAATCCT	360
CAAATTGCGG	CACATGTCAT	AAAGTGGGCC	AGCAGTAAAA	CAACATCTGT	GTTACAGTGG	420
GCTGAAAAG	GATACTACAC	CATGAGCAAC	AACTTGGTAA	CCCTGGAAAAA	TGGGAAACAG	480
CTGACCGTTA	AAAGACAAGG	ACTCTATTAT	ATCTATGCC	AAGTCACCTT	CTGTTCCAAT	540
CGGGAAGCTT	CGAGTCAAGC	TCCATTATA	GCCAGCCTCT	GCCTAAAGTC	CCCCGGTAGA	600
TTCGAGAGAA	TCTTACTCAG	AGCTGCAAAT	ACCCACAGTT	CCGCCAAACC	TTGCGGGCAA	660
CAATCCATTTC	ACTTGGGAGG	AGTATTGAA	TTGCAACCAG	GTGCTTCGGT	GTTGTCAAT	720
GTGACTGATC	CAAGCCAAGT	GAGCCATGGC	ACTGGCTTCA	CGTCCTTGG	CTTACTCAAA	780
CTCTGA						786

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 786 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

ATGATAGAAA	CATAACGCCA	ACCTTCCCCC	AGATCCGTGG	CAACTGGACT	TCCAGCGAGC	60
ATGAAGATTT	TTATGTATT	ACTTA	CTGT	CCCAAATGAT	TGGATCTGTG	120
CTTTTGCTG	TGTATCTCA	TAGAAGGTG	GACAAGATAG	AAGATGAAAG	GAATCTTCAT	180
GAAGATTTG	TATTGAA	AACGATAACAG	AGATGCAACA	CAGGAGAAAG	ATCCTTATCC	240
TTACTGAACT	GTGAGGAGAT	TAAAAGCCAG	TTTGAAGGCT	TTGTGAAGGA	TATAATGTTA	300
AACAAAGAGG	AGACGAAGAA	AGAAAACAGC	TTGAAATGC	AAAAAGGTGA	TCAGAATCCT	360
CAAATTGCGG	CACATGTCAT	AAAGTGGGCC	AGCAGTAAAA	CAACATCTGT	GTTACAGTGG	420
GCTGAAAAG	GATACTACAC	CATGAGCAAC	AACTTGGTAA	CCCTGGAAAAA	TGGGAAACAG	480
CTGACCGTTA	AAAGACAAGG	ACTCTATTAT	ATCTATGCC	AAGTCACCTT	CTGTTCCAAT	540
CGGGAAGCTT	CGAGTCAAGC	TCCATTATA	GCCAGCCTCT	GCCTAAAGTC	CCCCGGTAGA	600
TTCGAGAGAA	TCTTACTCAG	AGCTGCAAAT	ACCCACAGTT	CCGCCAAACC	TTGCGGGCAA	660
CAATCCATTTC	ACTTGGGAGG	AGTATTGAA	TTGCAACCAG	GTGCTTCGGT	GTTGTCAAT	720
GTGACTGATC	CAAGCCAAGT	GAGCCATGGC	ACTGGCTTCA	CGTCCTTGG	CTTACTCAAA	780
CTCTGA						786

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 864 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

AACTCTAACG	CAGCATGATC	GAAACATACA	GTCAACCTTC	TCCCCGCTCC	GTGGCCACTG	60
GACCACCTGT	CAGTATGAA	ATTTTATGT	ATTTACTTAC	AGTTTTCTT	ATCACCCAGA	120
TGATTGGGTC	AGCGCTTTT	GCTGTGTATC	TTCACAGACG	ATTGGACAAG	ATAGAAGACG	180

AAAGGAATCT	TCATGAAGAT	TTTGTGTTCA	TGAAAACGAT	ACAGAGATGC	AATAAAGGAG	240
AGGGGTCCCT	ATCCTTAUTG	AACTGTGAGG	AAATTAGAAG	CCGGTTTGAA	GACTTGGTCA	300
AGGATATAAT	GCAAAACAAA	GAAGTAAAGA	AGAAAAGAAAA	AAACTTTGAA	ATGCACAAGG	360
GTGATCAGGA	GCCTCAGATA	CGGGCACATG	TCATCAGTGA	GGCCAGTAGT	AAAACAACCT	420
CTGTTCTCCA	GTGGGCCCCC	AAAGGATACT	ACACCCTAAG	CAACAACCTG	GTAACCCTCG	480
AAAACGGGAA	ACAGCTGGCC	GTGAAAAGAC	AAGGATTCTA	TTACATCTAC	ACCCAAGTCA	540
CCTTCTGTT	CAATCGGGAA	ACTTTGAGTC	AAGCTCCATT	TATAGCCAGC	CTCTGCCTGA	600
AGTCCCAAG	TGGATCAGAG	AGAACCTTAC	TGAGAGCTGC	AAACACCCAC	AGTTCTTCCA	660
AACCATGCAG	GCAGCAATCC	ATTCACTTAG	GAGGAGTCTT	TGAATTGCAA	TCGGGTGCTT	720
CGGTGTTGT	CAATGTGACT	GATCCAAGTC	AAGTGAGCCA	CGGGACGGGC	TTCACATCAT	780
TTGGCTTACT	CAAACCTCTGA	ACGGTGTAAAG	CCAGCAGGCT	GCGGCTGGGC	TGATGCTGGT	840
GGTCTTCACA	ATCCAGGAAA	GCAG				864

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3634 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GAATTCCGGG	TGATTTCACT	CCCGGCTGTC	CAGGCTTGT	CTGCTACCCC	ACCCAGCCTT	60
TCCTGAGGCC	TCAAGCCTGC	CACCAAGCCC	CCAGCTCCTT	CTCCCCGCAG	GACCCAAACA	120
CAGGCCTCAG	GACTCAACAC	AGCTTTCCC	TCCAACCCGT	TTTCTCTCCC	TCAACGGACT	180
CAGCTTCTG	AAGCCCCCTCC	CAGTTCTAGT	TCTATCTTT	TCCTGCATCC	TGCTCTGGAAG	240
TTAGAAGGAA	ACAGACCACA	GACCTGGTCC	CCAAAAGAAA	TGGAGGCAAT	AGGTTTGAG	300
GGGCATGGGG	ACGGGGTTCA	GCCTCCAGGG	TCCTACACAC	AAATCAGTCA	GTGGCCCAGA	360
AGACCCCCCT	CGGAATCGGA	GCAGGGAGGA	TGGGGAGTGT	GAGGGGTATC	CTTGATGCTT	420
GTGTGTCCCC	AACTTCCAA	ATCCCCGCC	CCGCGATGGA	GAAGAAACCG	AGACAGAAGG	480
TGCAGGGCCC	ACTACCGCTT	CCTCCAGATG	AGCTCATGGG	TTTCTCCACC	AAGGAAGTTT	540
TCCGCTGGTT	GAATGATTCT	TTCCCGGCC	TCCTCTCGCC	CCAGGGACAT	ATAAAGGCAG	600
TTGTTGGCAC	ACCCAGCCAG	CAGACGCTCC	CTCAGCAAGG	ACAGCAGAGG	ACCAAGCTAAG	660
AGGGAGAGAA	GCAACTACAG	ACCCCCCTG	AAAACAACCC	TCAGACGCCA	CATCCCCTGA	720
CAAGCTGCCA	GGCAGGTTCT	CTTCCTCTCA	CATACTGACC	CACGGCTTCA	CCCTCTCTCC	780
CCTGGAAAGG	ACACCATGAG	CACTGAAAGC	ATGATCCGGG	ACGTGGAGCT	GGCCGAGGAG	840
GCGCTCCCCA	AGAACGACAGG	GGGGCCCCAG	GGCTCCAGGC	GGTCTTGT	CCTCAGCCTC	900
TTCTCCTTCC	TGATCGTGGC	AGGCGCCACC	ACGCTCTTCT	GCCTGCTGCA	CTTTGGAGTG	960
ATCGGCCCCC	AGAGGGAAGA	GGTGAGTGC	TGGCCAGCT	TCATCCACTC	TCCCACCCAA	1020
GGGGAAATGA	GAGACGCAAG	AGAGGGAGAG	AGATGGGATG	GGTAAAGAT	GTGCGCTGAT	1080
AGGGAGGGAT	GAGAGAGAAA	AAAACATGGA	GAAAAGACGGG	GATGCAGAAA	GAGATGTGGC	1140
AAGAGATGGG	GAAGAGAGAG	AGAGAAAGAT	GGAGAGACAG	GATGTCTGGC	ACATGGAAGG	1200
TGCTCACTAA	GTGTGTATGG	AGTGAATGAA	TGAATGAATG	AATGAACAAG	CAGATATATA	1260
ATAAAGATAT	GGAGACAGAT	GTGGGGTGTG	AGAAGAGAGA	TGGGGAAAGA	AACAAGTGTAT	1320
ATGAATAAAG	ATGGTGAGAC	AGAAAGAGCG	GGAAATATGA	CAGCTAAGGA	GAGAGATGGG	1380
GGAGATAAGG	AGAGAAGAAG	ATAGGGTGT	TGGCACACAG	AAGACACTCA	GGGAAAGAGC	1440
TGTTGAATGC	TGGAAGGTGA	ATACACAGAT	GAATGGAGAG	AGAAAACCG	ACACCTCAGG	1500
GCTAAGAGCG	CAGGCCAGAC	AGGCAGCCAG	CTGTTCTCC	TTTAAGGGT	ACTCCCTCGA	1560
TGTTAACCAT	TCTCCTCTC	CCCCAACAGTT	CCCCAGGGAC	CTCTCTCTAA	TCAGCCCTCT	1620
GGCCCAGGCA	GTCAGTAAGT	GTCTCCAAAC	CTCTTCTCA	ATTCTGGTT	TGGGTTTGGG	1680
GGTAGGGTTA	GTACCGGTAT	GGAAGCAGTG	GGGGAAATT	AAAGTTTGG	TCTTGGGGGA	1740
GGATGGATGG	AGGTGAAAGT	AGGGGGGTAT	TTTCTAGGAA	GTTTAAGGGT	CTCAGCTTTT	1800
TCTTTCTCT	CTCCTCTCA	GGATCATCTT	CTCGAACCCC	GAGTGACAAG	CCTGTAGGCC	1860
ATGTTGTAGG	TAAGAGCTCT	GAGGATGTGT	CTTGGAACTT	GGAGGGCTAG	GATTGGGGGA	1920
TTGAAGCCCG	GCTGATGGTA	GGCAGAACCTT	GGAGACAATG	TGAGAAGGAC	TGCTGAGCT	1980
CAAGGGAAGG	GTGGAGGAAC	AGCACAGGCC	TTAGTGGGAT	ACTCAGAACG	TCATGGCCAG	2040

GTGGGATGTG GGATGACAGA CAGAGAGGAC AGGAACCGGA TGTGGGTGG GCAGAGCTG 2100
 AGGGCCAGGA TGTGGAGAGT GAACCGACAT GGCCACACTG ACTCTCCTCT CCCTCTCTC 2160
 CTCCCTCCAG CAAACCCCTCA AGCTGAGGGG CAGCTCCAGT GGCTGAACCG CGGGGCCAAT 2220
 GCCCTCTGG CCAATGGCGT GGAGCTGAGA GATAACCAGC TGTTGGTGCC ATCAGAGGGC 2280
 CTGTACCTCA TCTACTCCCCA GGTCCTCTTC AAGGGCCAAG GCTGCCCTC CACCCATGTG 2340
 CTCCCTCACCC ACACCATCAG CCGCATGCC GTCTCCTTAC AGACCAAGGT CAACCTCCTC 2400
 TCTGCCATCA AGAGCCCCCTG CCAGAGGGAG ACCCAGAGG GGGCTGAGGC CAAGCCCTGG 2460
 TATGAGCCCCA TCTATCTGGG AGGGGTCTTC CAGCTGGAGA AGGGTGACCG ACTCAGCGCT 2520
 GAGATCAATC GGCCCCACTA TCTCGACTTT GCCGAGTCTG GGCAGGTCTA CTTTGGGATC 2580
 ATTGCCCTGT GAGGAGGACG AACATCCAAC CTTCCCAAAC GCCTCCCTG CCCAATCCC 2640
 TTTATTACCC CCTCCTTCAG ACACCCCTCAA CCTCTTCTGG CTCAAAAGA GAATTGGGGG 2700
 CTTAGGGTCG GAACCCAAGC TTAGAACTTT AAGCAACAAG ACCACCACTT CGAACACCTGG 2760
 GATTCAAGGA TGTGTGGCCT GCACAGTGAA GTGCTGGCAA CCACTAAGAA TTCAAACCTGG 2820
 GGCCTCCAGA ACTCACTGGG GCCTACAGCT TTGATCCCTG ACATCTGGAA TCTGGAGACC 2880
 AGGGAGCCTT TGGTTCTGGC CAGAATGCTG CAGGACTTGA GAAGACCTCA CCTAGAAATT 2940
 GACACAAGTG GACCTTAGGC CTTCCCTCTC CCAGATGTT CCAGACTTCC TTGAGACACG 3000
 GAGCCCAGCC CTCCCCATGG AGCCAGCTCC CTCTATTTAT GTTTGCACCT GTGATTATTT 3060
 ATTATTTATT TATTATTTAT TTATTTACAG ATGAATGTAT TTATTTGGGA GACCGGGGTA 3120
 TCCTGGGGGA CCCAATGTAG GAGCTGCCCT GGCTCAGACA TGTTTCCGT GAAAACGGAG 3180
 CTGAACAATA GGCTGTTCCC ATGTAGCCCC CTGGCCTCTG TGCCTCTTT TGATTATGTT 3240
 TTTTAAAATA TTTATCTGAT TAAGTTGTCT AAACAATGCT GATTGGTGA CCAACTGTCA 3300
 CTCATTGCTG AGCCTCTGCT CCCCAGGGGA GTTGTGTCTG TAATGCCCT ACTATTCACT 3360
 GGCGAGAAAT AAAGTTTGCT TAGAAAAGAA ACATGGTCTC CTTCTGGAA TAAATTCTGC 3420
 ATCTGCCTCT TCTTGTGGGT GGGAAAGAAGC TCCCTAAGTC CTCTCTCCAC AGGCTTTAAG 3480
 ATCCCTCGGA CCCAGTCCCA TCCTTAGACT CCTAGGGCCC TGGAGACCC ACATAAACAA 3540
 AGCCCAACAG AATATTCCCC ATCCCCCAGG AAACAAGAGC CTGAACCTAA TTACCTCTCC 3600
 CTCAGGGCAT GGGATTTCCT AACTCTGGGA ATTCA 3634

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1997 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GAGACAGAGT CTTGCTCTGT CCCCCAGGCT GGAATACAGT GGTGCGATCT TGACTCACTG 60
 CAGCCTCCGC CTCCCAGGTT CAAATAATTC TCCAGCCTCA GCCTCCCGAG TAGCTGGAC 120
 TGCAGATGCG CACCAGCACG CCTGGCTAAT TTTTGTATT ATTATAGAGA TGGGGTTTCA 180
 CCATGTTGGC CAGCTGGCT CAAACTCCTG ACCTCAAGTA ATCCGCCAC CTCAGACTCC 240
 CAAAGTGCCA GGATTACAGG TGTGAGCCAC TGCAACCAGGC CTGGAACAAT TTTAAAATAA 300
 TGTATTGGCT CTGCAAATGC AGTTCAAGAA CAAGTCCCTT AGCTGCCCC ACCCCACCC 360
 AAGTCACCCAC CCTTAAGCCT CACCCATGTG GAATTCTGAA ACTTCCTTTG TAGAAAACCTT 420
 TGGAAAGGTG CTGCCACATT GATCCTGGAA TGTGTGTTA TTTGGGGTTA TATAATCTG 480
 TTCTGTGGAA GCCACCTGAA GTCAGGAAGA GATGGAGGGC ATCCTTCAGG AGTGGAGATGA 540
 GACCTCATCA TACTTGACTG TCCAGCATCA TCTCTGAGTA AGGGGACCAA AAAATTATC 600
 TTCCAAACTA GGACACTTTC AAGAGTGAA GGGGGATCCA TTAATATTTT CACCTGGAC 660
 AGAGGCAAAAC ACCAGAAATGT CCCCAGTGA GGGGATATAT AATGGACCTT CTTGATGTGA 720
 AACCTGCCAG ATGGGCTGGA AAGTCCGTAT ACTGGGACAA GTATGATTTG AGTTGTTGG 780
 GACAAGGACA GGGGTACAAG AGAAGGAAAT GGGCAAAGAG AGAAGCCTGT ACTCAGCCAA 840
 GGGTGCAGAG ATGTTATATA TGATTGCTCT TCAGGGAAACC GGGCCTCCAG CTCACACCCC 900
 AGCTGCTCAA CCACCTCCTC TCTGAATTGA CTGTCCTTC TTTGGAACTC TAGGCCTGAC 960
 CCCACTCCCT GGCCCTCCCA GCCCACGATT CCCCTGACCC GACTCCCTT CCCAGAACTC 1020
 AGTCGCTGA ACCCCCCAGCC TGTGGTTCTC TCCTAGGCCT CAGCCTTTCC TGCCTTTGAC 1080

TGAAACAGCA	GTATCTTCTA	AGCCCTGGGG	GCTTCCCCGG	GCCCCAGCCC	CGACCTAGAA	1140
CCCGCCCCGCT	GCCTGCCACG	CTGCCACTGC	CGCTTCCTCT	ATAAAGGGAC	CTGAGCGTCC	1200
GGGCCCCAGGG	GCTCCGCACA	GCAGGGTGAAGG	CTCTCCTGCC	CCATCTCCTT	GGGCTGCCG	1260
TGCTTCGTGC	TTTGGACTAC	CGCCCGAGCAG	TGTCTGCC	TCTGCCTGGG	CCTCGGTCCC	1320
TCCTGCACCT	GCTGCCTGGA	TCCCCGGCCT	GCCTGGGCCT	GGGCTTGGTG	GGTTGGTTT	1380
TGGTTTCCCT	CTCTGTCTCT	GACTCTCCAT	CTGTCAGTCT	CATTGTCTCT	GTCACACATT	1440
CTCTGTTCT	GCCATGATTC	CTCTCTGTC	CCTTCCTGTC	TCTCTCTGTC	TCCCTCTGCT	1500
CACCTTGGGG	TTTCTCTGAC	TGCATCTTGT	CCCCTTCTCT	GTCGATCTCT	CTCTCGGGGG	1560
TCGGGGGGTG	CTCTCTCCCA	GGGCGGGAGG	TCTGTCTTCC	GCCGCGTGCC	CCGCCCCGCT	1620
CACTGTCTCT	CTCTCTCTCT	CTCTTTCTCT	GCAGGTTCTC	CCCATGACAC	CACCTGAACG	1680
TCTCTTCCTC	CCAAGGGTGT	GTGGCACAC	CCTACACCTC	TCCCTTCTGG	GGCTGCTGCT	1740
GGTTCTGCTG	CCTGGGGCCC	AGGTGAGGCA	GCAGGAGAAT	GGGGGCTGCT	GGGGTGGCTC	1800
AGCCAAACCT	TGAGCCCTAG	AGCCCCCCTC	AACTCTGTC	TCCCCTAGGG	GCTCCCTGGT	1860
GTTGGCCTCA	CACCTTCAGC	TGCCCAGACT	GCCCGTCAGC	ACCCCAAGAT	GCATCTTGCC	1920
CACAGCACCC	TCAAACCTGC	TGCTCACCTC	ATTGGTAAAC	ATCCACCTGA	CCTCCAGAC	1980
ATGTCCCCAC	CAGCTCT					1997

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10240 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GAATTCCCCG	GATCAAAGTC	AGCATTAAAT	CCCAGTTTAG	GTTTGAGGGC	TAAGTTCAAG	60
TTTGAGTCTA	ATGTCATTTC	AGCCTGTTT	GGAGGAAC	GAGATTCAC	TAGTTCTCC	120
GCAGAGACCA	CTGTAGAAC	TGCATTTCCC	TGAGTTTGG	GCACAAGACT	CCAGTCATCA	180
CCCCTCCAC	ACAGGGAAAG	CCCCAAACCA	ACTGCTGGCC	TCCTCAAGAA	AGAAAACCGAA	240
TTTCACACAA	CCTCCGAAAC	TAAGATTGAA	ACCAAGATTG	GCCCCATCTCA	AGGCGCGTCC	300
TCCAGCACAT	TGAGAATGTC	GCTGATGGAG	CCTCGGCCA	GCTCTCGAGC	TTCTTCCTT	360
TCTGTCTCTC	ATGTCCTCTC	ATCACTCCTT	CTCACCTTCC	CGTTTTGTC	CTGCAATGCC	420
CCCTTCTTCC	TCTCTTCCTG	GGGTTTTCC	CTTATTTC	CACTGTACCA	TTTTATATTT	480
TAATAAAGCC	GAGGTCTCCT	AGTCCATCAG	CTCCTACTGT	TGGAGAGGAG	GCAGAAAGAA	540
ACAGCAGGAC	GGCAAAGGGA	CTCCAGAGAA	AGAGACTCAG	AGGAAAGGCA	AGAAACAGGG	600
ACCAAGAGAG	AGGCCAACAG	TGACACAAGA	CACAGTGAGG	TTAAAAGAAA	TAAGATGAGG	660
CCAAGATAGA	GACCAAGCTA	TTTAAAAGAG	CCATCTGTGG	CTACCTCTCT	TCCGCCATCG	720
CATCTGGTCA	GCCACCAAGA	TTTTGCCTAG	AAACGTTCT	CCTCTCCATT	CTCCTGCTGC	780
TGCTGCTGCT	GCTGCTGCTG	CTGCTGCTGC	TGCTGCTGCT	GCTGCTGCTG	CTGCCCTTAAT	840
ACGAATGCGAG	GCTCTTGTCA	TCTCCTTGCT	GGGTTGTTGC	AAAATCCTCC	TAACTGGTCT	900
CCACACTTCT	CATTCCCCT	CCAGCCCCC	ATCTCCATA	CTTCCATTTA	TTTATTGTTGG	960
CCATGCCCAT	GGCATGTGGC	AGTTCCAGGG	GCCAGGGATC	AAACCTGTGC	CAATGCAGTG	1020
ACCGTGTCA	ATCCTTAACC	CACTGCACAC	AAGGCAACGC	CCCTCGAGTC	ATTCTCATTT	1080
TTTAAATATA	CCAATTGAG	GGGGTCCCTC	TTTCACTTAA	AAATTTGGC	AGCTCCCTAT	1140
CATGATGAGA	AGGAATTCCA	AACCATTTC	CTTGTGTGCA	AACCCCTCAG	CATGTGTCT	1200
CAGCTTACTT	CCCAAGCCTC	ATCCCTGTC	CTTCTACGTG	TACCCATGTG	TACATCTCCA	1260
CACACCATAT	ACTCTTTTT	ACCTCCCATC	TTTGCACCTT	CTGTTCCCTC	TCTCTGCC	1320
TCACCATCTT	TTTGCTTTG	ATACTTAATG	CCTCTCCCTC	AGGCCAGGTT	CAATGGCTTT	1380
TCTGTGGGCT	GCTTTAAGCC	CACTGTCTG	GAACATTATCA	CATTTTATTT	TATTGACTT	1440
TCTTTTTAGG	GCCGCACCCA	GCATATGGAG	ATTCCCAAGGC	TAGGGATCTA	ATCGGAGCTG	1500
TATCTGCCAG	CCTGCGCTGG	AGCCACAGCA	ACGTGGGATC	CGAGCCTGAG	GGGTTTGAT	1560
GTCCTGTGGC	ACAGAACGTTA	CATTCAGGCT	GTGCATGAAC	TATTCTCCT	GTTCTCCTCC	1620
CCCTGCTTGA	GGCCCTGCA	CTTGCCTCT	CATGCCCTG	TGCTCTGACC	TATGACTTCT	1680
TTTGTTTGC	ATTCCATCTC	TTTAGTTTC	TCTCTGTTCC	ACAAACATT	ACTGAGCATC	1740
TACATGAGGC	ATTGAGGATA	CGGATGGAA	AGACAGTCCC	CTGACCTCTG	GGACCTCAAA	1800
GACCAATTGT	GGAAGACTGG	TTGGTTATCA	GATAATTACA	ATGAAGTGTG	GGAGTCCCTG	1860

TCATGGGTCA	GCAGGTAATG	AACCCAGTAA	ACGATCCATG	AGGATGCAGA	TTCAATCCCT	1920
GCCCTTGCTC	AGCGGGTTAA	GGATCCAGCG	TTCCCACAAG	CTGTGGGTGA	GGTCGCAGAT	1980
GCGACTCAGA	TCTTGCATTG	CTGTGGCTGT	GGTAGGCT	GGTGGCTACC	CCTAGCCTGG	2040
GAACCTCCAT	ATGCCCTCAGG	TGCGGCCCTA	AAAGACAAAAA	AAAAAAAAGA	GAGAAACTTT	2100
TCTTTTCTT	AATGTGTAAC	CTACAAGCTA	AGTGAAAACT	GGCTCCTATT	CCATAACGTT	2160
TGTATCATT	TTCATACTAG	CCAAATACTA	GAAACAGGGA	GTTCCTCG	TGGTGCAGCA	2220
GAAACAAATT	CGACTAGGAA	CCATGAGGTT	GC GG GTT CGA	TCCCTGGCCT	TGCTCAGTGG	2280
GTIAAGGATC	CGGCGTTGCC	GTGAGCTGTG	GTGAGGTGCG	CAGATGTGGC	TCGGATCTAG	2340
TGTTGCTGTG	GCTCTGGTGT	AGGCCGGCAG	CAACAGCTCT	GATTAGACTC	CTAGCCTGAG	2400
AACCTCCATA	AGCTGTGGCT	GGGGCCCTAT	AAAGACAAAAA	AAAAAAAAGA	GGCAAATAC	2460
TAGAAACAAA	CCAAATGCC	ATCAACAGAA	GAATAGATAA	GTAAATTGGG	GTATATGCAC	2520
ACAATAGCAT	CACACAATAA	CATGCACACA	ATAACATCAC	AATGAAATAA	AAATTACTAC	2580
TGACAGACAC	AACCATA TAG	ATGAATTCA	CAAACACAAC	AGCGAGAATA	AAAGCCAAGC	2640
ACAGATGAGT	TGTCTGTGTG	GATTCA TT C	TATGAAGTT	AAGCGCAGGA	AGAACTTAAT	2700
CTATAGTGAC	AGAGGTCAGA	GAGCAGTTGG	TTGTC TTT GG	CAGGTATGAA	CTGGGAGTGG	2760
GCATGAGAGA	ACTTTCTGGA	GACCTAAAAA	TATATTGGAC	TGGATGGTGG	CAACATGGCT	2820
ACAAGAAGAT	GGAAAAGTTC	CTCAGGCTGT	CCACTTGGGA	GACGGGCTTC	TCACGGGACC	2880
TAAGTTCTGC	ATCAGCAGAG	GGGGAAATCC	TTAATGATT	GACAATTACA	AAGTGTATTG	2940
GCTTTACCGA	TGTATTTCA	ACACAATCCC	TCTGCTGTCC	CCACCCCCACC	CTAGGTCACC	3000
ACCCTTAAGC	TCCACCTGTG	TGGAATTCTG	AAGCCTCCCC	TGTAGAGAAC	TTTAGCAGTT	3060
GCCACGTTCT	TTTGATGCAG	GAACGTGTTG	TCTAGAGTTA	GACACATCTG	ATCTGTGGGG	3120
CCCACCCAAG	GTG G G G ACAT	GGTGGGGGGC	GGCCTTCTGC	AGTGAGATGA	AACCTCATTG	3180
TAGGTGATT	CGTGGCCTCA	TCCCTGAGTC	AGATCTTCCA	AATGAGGACA	CTTGGGAGAG	3240
CAAAAGGGGG	CTCCCTGAAG	ATTTCCCTCA	GGACAGCAGG	AACAAACCA	GATGTCCCAG	3300
GCAGGAGGGT	ATAGAAGGGA	ACTTGTGAT	ATGAAATCAG	CCAGATGACC	TGGAAAATAC	3360
ACAGACTGGG	ACAAGTGTGA	CTTGAGCCTC	TTGGGCCCAG	GACAGGGGTA	CAGAGGAGGA	3420
AACGTGCACA	GAGAGAAGCC	CGTAATCAGC	CAAGGCTGCA	GAGGTGTTAT	ACATAATCGC	3480
TCTTCACGCA	ACCGGGCAAG	CAGCCCACGC	CCCAGCTGCA	CTCCATCTCC	TCCTCTGAAC	3540
TCACCGTCCC	TTCTCTGGAA	CTCCTAAGCC	TGACCCCGCT	CCCTGGCCCT	CCCAGCCCAC	3600
GGTTCCCCTG	ACCCC ACTCC	CTTTCCCAGA	ACTCAGTCAT	CTGAGCCCCC	AGCCTGC GTT	3660
CTCTCCTAGG	CCTCAGCCTT	TCCTGCCTTC	CGGTGAAACA	GCAGCATCTT	CTAAGCCCTG	3720
GGCTTCCCCA	GGCCCCAGCC	CCGGCCTAGA	ACCCGCCCAG	CCGACCTGCC	CACGCTGCCA	3780
CTGCCGGCTT	CCTCTATAAAA	GGGACCCAGG	GCGCC CAGAA	AGGGGCCAC	AGGGGTCCCAG	3840
CACAGCAGGT	GAGACTCTCC	CACCCCATCT	CCTAGGGCTG	TCCGGGTGCT	GGACTCCCCC	3900
CTCACTTCGG	TCCCTCCGCC	CGCTCCCTGG	CCTTCCTGCC	CCTCCTGCAT	CTTCACCCCC	3960
GCCTGGGCCT	TGGTGGGTTT	GGTTTTGGTT	TGTTCTCTCT	GATTCTTAT	CTGTCAGGCT	4020
CTTTCTAGCT	CTCACACACT	CTGATCCCTC	TCTGTTCCCT	TCCCATCTCT	GT TCTCTCT	4080
GGGTCTCCCC	CTGCTCACCT	CGGGATTTC	CTGAGTGCCT	CTGGTCCCCC	TCTCTGTCTG	4140
GCGCCCCGTC	TCTTGTCTCT	CGGGGTGGCT	GTCTCCGAGG	GCAGGAGGCC	TTCTTCCGCA	4200
GGTCCCCCGC	CCCGCTCACT	GTCTCTCTCC	CCCCACAGGT	TTTCCCCATG	ACACCACTG	4260
GACGCCCTA	CCTCCGGAGG	GTGTGCAGCA	CCCCCATCCT	CCTCCTCCTG	GGGCTGCTGC	4320
TGGCCCTGCC	GGCCCGAGGCC	CAGGTGAGGC	AGCAGGAGAG	CGGGCCGTGG	GGGCAGCCTT	4380
CGCCAACCTT	GGGCCTCAGA	GCCTCTCTGA	CGCTCTTCTC	CCCTAGGGGC	TCCCTGGCGT	4440
CGGCCTCCCA	CCCTCAGCTG	CACAGCCTGC	CCATCAGCAC	CCCCCAAAGC	ACTTGGCCAG	4500
AGGCACCCCTC	AAACCTGCCG	CTCACCTCGT	TGGTAAACAT	CCACCTGGCC	TCCCAGACCT	4560
GTAGCCCCCA	GTCCTCCTCC	TATGCCCTG	CTTCAGGGAC	TGAAGCATCC	CTCCCCCCCCA	4620
TCTCCCCCCA	CCCCCTAAAT	GGAGGCATCC	CACTCCCAGC	TCCCTCCCAA	CCATCCCCCA	4680
GGA ACTCAGT	CCAGCACCTG	CTTCCTCAGG	GATTGAGACC	TCCGACCCCC	AGGTCCCTTGA	4740
CTCCCCACCC	CTCTGGCTCT	TCCTAGGAGA	CCCCAGCACC	CCGGACTCAC	TGGCCTGGAG	4800
AGCGAACACG	GATCGTGCCT	TCCTCCGCCA	TGGCTTCTTG	CTGAGCAACA	ACTCCCTGCT	4860
GGTCCCCACC	AGTGGCCTCT	ACTTTGTCTA	CTCCCAGGTC	GTCTTCTCCG	GGGAAGGCTG	4920
CTTCCCCAAG	GCCACCCCCA	CCCCCTCTCA	CCTGGCCCTAC	GAGGTCCAGC	TCTTCTCCTC	4980
CCAGTACCCC	TTCCACGTGC	CGCTCCTCAG	CGCTCAGAAC	TCCGTGTGCC	CCGGGCCACCA	5040
GGGACCTTGG	GTGCGCTCTG	TGTACCAAGGG	GGCTGTGTT	CTGCTCACCC	AGGGAGATCA	5100
GCTGTCCACA	CACACAGACG	GCACCCCCCA	CCTGCTCCTC	AGCCCCAGTA	GC GTCTTCTT	5160
TGGAGCCTTC	GCTCTATAGA	AGAATCCAGA	AAGAAAAAAA	TTGGTTCAA	GGCCTTCTCC	5220
CCTTTTCA CC	TCCCTTATGA	CCACTTCGGA	GGTCACCGCG	CCTCTCCCT	GACAATTTC	5280
AACAGTCTCA	TCTTCCCCCA	CGCTCAGCAC	CTGGAGCTTC	TGTAGAAGGA	ATTCTAGGCA	5340
CCTCGGGGGA	ACTGGAACCA	CCCCGGATGC	TCTGCTGAGG	ATCTGAATGC	CCGCCTGGAG	5400
CCCTCCCCCT	GTCCTGCCCG	TCTAGGGGCC	CTCGTCCAGG	ACGTGGAAGG	GAAGCTGACC	5460

CATGAGGGAC	TTTGAACGGA	TGACCGGAGC	GGTGTGGGGG	GGTTATTAT	GAAGGGGAAA	5520
ATTAATTAT	TTATTATATGG	AGGATGGAGA	GAAGGGAAATC	ACAGAGGGAT	GTCAGAACAG	5580
TGTGACACAT	GTGCCAAGA	GATAAAGTGA	CAGAAGGCAT	GGGCTCCAGA	TGACCCGGCC	5640
AGAGAGGGCA	AAGTGGCTCA	CCAAGGGGCT	GCTTGACTGG	AGGCTCATGA	GGAGACGGCT	5700
GACCCCTCGAT	GAAACCCAAT	AAAGCTCTT	TCTCTGAAAT	GCTGTCTGCT	CGTATCTGTC	5760
ACTCGGGAGG	GGAGAATTCT	CCAGATGTCT	CTAAGGAGTG	GAGGGAGGAC	AGGAATCAGA	5820
GGGGACGGGA	GCTGTGGGTG	TGTGATGAGG	CCTAAGGGGC	TCAGGTGAGA	GATGGCGGCC	5880
TCAGGGGTAG	GGCAGCCAGA	CCCCCTGCAGG	AGAAGCAGAT	GGTTCCCTTG	AGAAGACAAA	5940
GGAAGAGATG	CAGGGCCAAG	GTCTTGAGAA	CCGAGGTGCG	GGGTGCGCTG	GCAGATATGG	6000
CCACAGGTAG	AGGGACAGAG	GAATAGGGT	GACAGGAGGC	TTCGGGGAG	AAGGAAACAC	6060
ACTGAGGGGT	GTTCGGGATT	CTGAGGGAGG	AGCACGGGA	CGCCCTGGGA	GACATGCCGT	6120
CCAGGGCCAT	GAGGAGTGGG	AGAGCCTCTG	AGGCTAGCGG	CTGGAGATAC	AGGGACATTT	6180
GAGGAGACAC	GGTCATGGCC	AGGAGCCGCG	AGGGCTGGA	CAGTCTCTAG	GAATCTCGAA	6240
GAAGCAGGAA	TTCTTGAGG	ATACGTGGCC	ACACAAAGGG	AGGCTGAGGT	GTGGGGACTT	6300
CATGCAGAAAG	TCAGGGCCTC	ACATTCCTT	GGAAAGCCAG	ACTGAAACCA	GCAGCAGAGT	6360
TTTGGTGAGT	TCCTGTCAGA	GTGAAAGGAG	AAGGCCCAGC	ATGGTGGGTT	TGTGAATTCC	6420
CAGCCTGGCT	TCCTCTCCCT	CTGGGCTGT	CCCAGGCCTG	TTCCTGCCGT	CCTCCCCCAG	6480
CCCGTGTAGG	GCCTCCAGCT	GCCCTCTCC	CAGCTCCTCT	TCCCTCCAGG	AGACGAAACA	6540
TGGGTCTCAG	CACCCAGCAG	GGTGTGCTCT	AAGTTTCTC	TCCATTAAGA	ACTCAGCTTT	6600
CTGAAGCTCC	TCCCATTCCCT	AGTTCTACCC	CTACCTGAGC	CCTGTTCGGA	AATCAGAGAG	6660
AAATAGAAGT	CATCCCCCAA	AGAAAAGGAA	TTTGTCCCCC	AAAGAAACAG	AACTTGTCCC	6720
CCAAAGAAAT	GGAAACAAATG	GGAAATGGGA	GGCAGGGGGG	ACCTGGGTC	CAGCCTCCAG	6780
GGTCCTACAC	ACAGAGCAGT	AACTGGCCA	GCAAGCCCAC	CTCAGGATCC	GGGCAGGGAG	6840
GGTAGGAAGT	ATCCCTGATG	CCTGGGTGTC	CCCAACTTTC	CAAACGCCG	CCCCCGCTAT	6900
GGAGATGAAA	CTAAGACAGA	AGGTGCAGGG	CCCGCTACCG	CTTCCTCCAG	ATGAGCTCAT	6960
GGGTTTCTCC	ACCAAGGAAG	TTTCCGCTG	GTTGAAAGAG	AGCCTCTCCC	CGCCCTCTTC	7020
TCACCCAGAG	CGTATAAAATG	CAGCTGTTG	CACACCCAGC	CAGCAGAACG	TCCCAGAGTG	7080
AGGACACCAG	GGGACCAGCC	AGGAGAGAGA	CAAGCCATCT	CCAGGACCCC	CTAGAAATAA	7140
CCTCTCAGAA	GACACACCCCC	CGAACAGGCA	GCCGGACGAC	TCTCTCCCTC	TCACACGCTG	7200
CCCCGGGGCG	CCACCATCTC	CCAGCTGGAC	CTGAGCCCC	CTGAAAAGA	CACCATGAGC	7260
ACTGAGAGCA	TGATCCGAGA	CGTGGAGCTG	CGGGAGGAGG	CGCTCGCAA	GAAGGCCGGG	7320
GGCCCCCAGG	GCTCCAGGAG	GTGCCTGTG	CTCAGCCTCT	TCTCCTTCT	CCTGGTCGCA	7380
GGAGCCACCA	CGCTCTTCTG	CCTACTGAC	TCAGGTTA	TCGGCCCCA	GAAGGAAGAG	7440
GTGAGCGCCT	GGCCAGCCTT	GGCTCATTCT	CCCACCCGGA	GAGAAATGGG	GAAGAAAGAG	7500
GGCCAGAGAC	GAGCTGGGG	AAAGAAGTGT	GCTGATGGGG	AGTGTGGGGA	GGAAATCATG	7560
GAGAAAGATG	GGGAGGCAGA	AGGAGACGTG	GAGAGAGATG	GGGGAGAGA	GAGAAGGATG	7620
GAGAGAAATC	CGGTGGCCCG	GCCCTTGGAA	ATGCTCTCTA	ATATTTGTT	GCACGAATGA	7680
GTGAGTAAGC	AGGGACACCG	ATATAAAGAG	AGATGAGTAG	ACAGACAAGG	GGTGTGGTAG	7740
AAAGATAGGG	AAAAAACAAAG	TGATCTGGAT	AAAGATAGTG	AGACAGGAAG	AGGTAGAGGA	7800
GATAGGAAAG	AGAGATAAGG	AGAGAAGAAG	GAAGCGTGGG	TGTCTGGCAC	GTGGAAGGCA	7860
CTCAATGAAG	GAGTTGTTGA	ATGGATGGGT	GGATGAGAAA	ATGGATGAGT	GGAGAGAAAA	7920
AACTAGACAT	CAGGGCAGAG	AGTACAAGCT	AGAGAACGAG	GTGGCTGTT	TCCCTTCAGA	7980
GGGGACTTAT	TCAAATCTAA	TTAATCCTTC	TTCTCTCC	CAACAGTTTC	CAGCTGGCCC	8040
CTTGAGCCTC	AACCCCTCTGG	CCCAAGGACT	CAGTAAGTAT	CTCTAAAACC	TGTCTCTCAG	8100
TTCTGAGCTT	GGACAGGGGT	GGGGTTAGTG	CTGGGGTGG	AGGAAGAAGG	GAATTAGG	8160
GTCTGGGTTT	GGCGGGGGGA	ATGCAGGTCA	AAGTAGTGTG	ATATTTCTG	GGAAAGTCTGA	8220
GGGTCTCATC	TTTTCTTTC	CTCTTCTTC	CTCAGGATCA	TCGTCTCAA	CCTCAGATAA	8280
GCCCGTCGCC	CACGTTGTAG	GTAAGAGTTC	TGAGGATGTG	TCTGGGGAT	GAAGAAATAG	8340
GCAGGACAGA	GACGGATAGG	ATTGGGGGGC	TGAAGCCAGG	CTGAGGGTAG	CCAGAGCTTG	8400
GAGATAGTAT	GAGGAGGACT	CGCTGAGCTC	CAGGGGAGGA	TGGGGATAC	TCAGAACTTG	8460
AGGAGGATAC	TCGGAACCTC	ATGGACAGAT	GGGATGTGGG	AAGACAGACC	GAGGGGACAG	8520
GAACCGGATG	TGGGGGGCGG	GCAGAACTCG	AGGGCCAGGA	TGTGGAGAGT	GGAACTGACA	8580
GGGTACACT	GACTCACCCCC	TCCCTCTTGT	TCTCCTCCCT	CCAGCCAATG	TCAAAGCCGA	8640
GGGACAGCTC	CAATGGCAGA	GTGGGTATGC	CAATGCCCTC	CTGGCCAACG	GCGTGAAGCT	8700
GAAAGACAAAC	CAGCTGGTGG	TGCCGACAGA	TGGGCTGTAC	CTCATCTACT	CCCAGGTCT	8760
CTTCAGGGGC	CAAGGCTGCC	CTTCCACCAA	CGTTTCTCTC	ACTCACACCA	TCAGCCGCAT	8820
CGCCGTCTCC	TACCAGACCA	AGGTCAACCT	CCTCTCTGCC	ATCAAGAGCC	CTTGGCCAGAG	8880
GGAGACCCCC	GAGGGGGCCG	AGGCCAAGCC	CTGGTACGAA	CCCATCTACC	TGGGAGGGGT	8940
CTTCCAGCTG	GAGAAGGATG	ATCGACTCAG	TGCCGAGATC	AACCTGCCCG	ACTATCTGGA	9000
CTTGCTGAA	TCTGGCAGG	TCTATTTGG	GATCATTGCC	CTGTGAGGGG	GCAGGACATC	9060

CGTTCCCTCC	CCTGTCCATC	CCTTTATTAT	TTTACTCCTT	CAGACCCCT	CACGTCCCTC	9120
TGGTTTAGAA	AGAGAATGAG	GGGCTGGGA	CTGGGCTCCA	AGCTTAAAAC	TTTAAACAAC	9180
AACAGCAACA	CTTAGAAATC	AGGGATTCA	GGATGTGTGG	CCTGGACAAC	CAGGCAC	9240
CCACCACCAA	GAATTGGAAC	TGGGGCTTCC	AGACTCGCTG	GGGTCCCTGG	GTTTGGATT	9300
CTGGATGCAA	CCTGGGACAT	CTGGAATGTG	GCTGCCAGGG	AAGCTTG	TCCAATCGGA	9360
ATACITCAGA	ACATTCCTG	AGAAGATTTC	ACCTCAATCT	TGATGACTT	TTAGGCTTCC	9420
CTTTCTTCCA	ATTTTCCAGA	CTTCCCTGGG	ATGGGGAGCC	CAGCCCCAA	CCCCACAGGC	9480
CAGCTCCCTC	TTATTATAT	TTGCACTTGG	CATTATTATT	TATTTATT	TTTATTATTT	9540
ATTTACTAGT	GAATGTATT	ATTCAAGGAGG	GCGAGGTGTC	CTGGGAGACC	CAGCATAAGG	9600
GCTGCCTTGG	TTCAGATGTG	TTTTCTGTG	AAACGGAGCT	GAACGTAGG	TTGCTCCCAC	9660
CTGGCCTCCT	AGCCTCTGTG	CCTCCTTGT	CTTATGTTT	AAAAAACAA	TATTTATCTG	9720
ATCGAGTTGT	CTAAATAATG	CTGATTG	GACTAACTTG	TCGCTACATC	GCTGAACCTC	9780
TGCTCCCCAG	GGGAGTTGTG	TCTGTAACCG	CCCTACTGGT	CAGTGGCGAG	AAATAAAAGC	9840
GTGCTTAGAA	AAGAAATCTG	GCCTCTTCT	GCGACTGAAT	TCTGCATCTC	CTTGGGGGGG	9900
TGAGGCTGCT	CCCCAAAATT	CTTTCTCCAC	CGGGCTTAGG	ATTCCCTGGG	CTTCAC	9960
GAGCTTGGAC	TGCCTGGCTC	AGGAGCCTCT	GCAAGAAACA	AAGCCCAGCC	AAACAGGTCC	10020
CTCCCCTAAG	AAAGGAACCT	GAAGGTAATT	ACCTCTCCCT	CAGGGTGTGG	GAATTCCAA	10080
GTCTGGGAAT	TCCTATCCAG	CTGGGGAAAGT	CTGCAGTGC	GGTGAGACTT	CCGGCTGAAA	10140
GAGCCAGGGA	GCGGCCAGAT	GCTCAGGTAC	CTGAACCAGA	GCCAAGGGAC	TTCCAGACAG	10200
TGAGGCAACT	GGGCTCCAAA	TAACCTGATC	CGGGGAATT			10240

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1644 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

CCTCAGCGAG	GACAGCAAGG	GA	CTAGGCCAG	GAGGGAGAAC	AGAAACTCCA	GAACATCCTG	60	
GAAATAGCTC	CCAGAAAAGC	AAGCAGCCAA	CCAGGCAGGT	TCTGTCCCTT	TCAC	ACTCACTG	120	
GCCCAAGGCG	CCACATCTCC	CTCCAGAAA	GACACCATGA	GCACAGAAAG	CATGATCCGC	180		
GACGTGGAAC	TGGCAGAAGA	GGCA	CTCCCC	CAAAGATGG	GGGGCTTCCA	GAAC	TCAGG	240
CGGTGCCTAT	GTCTCAGCCT	CTTCTCATTC	CTGCTTGTGG	CAGGGGCCAC	CACG	CTCTTC	300	
TGTCTACTGA	ACTTCGGGGT	GATCGGTCCC	CAAAGGGATG	AGAAGTCCC	AAATGGC	CTC	360	
CCTCTCATCA	GTTCTATGGC	CCAGACCC	TCAC	TCAGAT	CATCTCTCA	AAATTCGAGT	420	
GACAAGCCTG	TAGCCCACGT	CGTAGCAAAC	CACCAAGTGG	AGGAGCAGCT	GGAG	TGGCTG	480	
AGCCAGCGCG	CCAACGCCCT	CCTGGCCAAAC	GGCATGGATC	TCAAAGACAA	CCA	ACTAGT	540	
GTGCCAGCCG	ATGGGTTGTA	CCTTGTCTAC	TCCCAGGTTC	TCTTCAGGG	ACAAGG	CTGC	600	
CCCGACTACG	TGCTCCTCAC	CCACACCGTC	AGCCGATTG	CTATCTCATA	CCAGG	AGAAA	660	
GTCAACCTCC	TCTCTGCCGT	CAAGAGCCCC	TGCCCCAAGG	ACACCCCTGA	GGGG	GCTGAG	720	
CTCAAACCCCT	GGTATGAGCC	CATATACCTG	GGAGGAGTCT	TCCAGCTGGA	GAAG	GGGGAC	780	
CAACTCAGCG	CTGAGGTAA	TCTGCCAAG	TACTTAGACT	TTGCGGAGTC	CGGG	CAGGTC	840	
TACTTGGAG	TCATTGCTCT	GTGAAGGGAA	TGGGTGTTCA	TCCATTCTCT	ACCCAG	CCCC	900	
CACTCTGACC	CCTTTACTCT	GACCCCTTA	TTGTC	ACTC	CTCAGAGCCC	CCAGTCTG	960	
TCCTTCTAAC	TTAGAAAGGG	GATTATGGCT	CAGAGTCCAA	CTCTGTG	CTC	AGAGCTTCA	1020	
ACAACACTC	AGAAACACAA	GATGCTGGGA	CAGTGACCTG	GACTGTGGC	CTCTCATG	CA	1080	
CCACCATCAA	GGACTCAAAT	GGGCTTCCG	AATTCA	TGG	AGCCTCGAAT	GTC	1140	
GAGTTCTGCA	AAGGGAGAGT	GGTCAGGTG	CCTCTGTCTC	AGAATGAGG	TGGATA	AGAGT	1200	
CTCAGGCCTT	CCTACCTTCA	GACCTTCCA	GACTCTCCC	TGAGGTGCAA	TG	CACAGCCT	1260	
TCCTCACAGA	GCCAGCCCCC	CTCTATT	ATTGCA	TTT	AAATTTT	ATTATTTAT	1320	
TATTTATT	TTTGCTTATG	AATGATT	TTTGGAAAGG	CGGGGTG	TGGAGG	ACCC	1380	
AGTGTGGGAA	GCTGTCTCA	GACAGACATG	TTTCTGTGA	AAACGGAGCT	GAGCT	GTCCC	1440	
CACCTGGCCT	CTCTACCTTG	TTGCCTCC	TTTGCTTAT	GT	TTAAAACA	AAATATT	1500	
CTAACCAAT	TGTCTTAATA	ACGCTGATT	GGTGACCAGG	CTGTCGCTAC	ATCA	CTG	1560	

CTCTGCTCCC CACGGGAGCC GTGACTGTAA TTGCCCTACA GTCAATTGAG AGAAATAAAG 1620
ATCGCTTAAA ATAAAAAAACC CCCC 1644

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1890 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

AAACAGAGAG	AGATAGAGAA	AGAGAAAAGAC	AGAGGGTGT	CCCTTAGCTA	TGGAAACTCT	60
ATAAGAGAGA	TCCAGCTTGC	CTCCTCTTGA	GCAGTCAGCA	ACAGGGTCCC	GTCCTTGACA	120
CCTCAGGCC	TACAGGACTG	AGAAGAAGTA	AAACCCTTGTG	CTGGGGCTGG	CCTGACTCAC	180
CAGCTGCCAT	GCAGCGAGCC	TTCAATTACC	CATATCCCCA	GATCTACTGG	GTGGACAGCA	240
GTGCCAGCTC	TCCCTGGGCC	CCTCCAGGCA	CAGTTCTTCC	CTGTCCAACC	TCTGTGCCCA	300
GAAGGCCTGG	TCAAAGGAGG	CCACCACAC	CACCGCCACC	GCCACCACTA	CCACCTCCGC	360
CGCCGCCGCC	ACCACTGCCT	CCACTACCGC	TGCCACCCCT	GAAGAAGAGA	GGGAACCACA	420
GCACAGGCCT	GTGTCTCCTT	GTGATGTTT	TCATGGTTCT	GGTTGCCCTG	GTAGGATTGG	480
GCCTGGGGAT	GTTCAGCTC	TTCCACCTAC	AGAAGGAGCT	GGCAGAACTC	CGAGAGTCTA	540
CCAGCCAGAT	GCACACAGCA	TCATCTTGG	AGAAGCAAT	AGGCCACCCC	AGTCCACCCCC	600
CTGAAAAAAA	GGAGCTGAGG	AAAGTGGCCC	ATTAAACAGG	CAAGTCCAAC	TCAAGGTCCA	660
TGCCTCTGGA	ATGGGAAGAC	ACCTATGGAA	TTGTCTCTG	TTCTGGAGTG	AAGTATAAGA	720
AGGGTGGCCT	TGTGATCAAT	GAAACTGGC	TGTACTTTGT	ATATTCCAAA	GTATACTTCC	780
GGGGTCAATC	TTGCAACAAAC	CTGCCCTGA	GCCACAAAGGT	CTACATGAGG	AACTCTAAGT	840
ATCCCCAGGA	TCTGGTGTATG	ATGGAGGGGA	AGATGATGAG	CTACTGCACT	ACTGGGCAGA	900
TGTGGGGCCCG	CAGCAGCTAC	CTGGGGGCAG	TGTTCAATCT	TACCACTGCT	GATCATTAT	960
ATGTCAACGT	ATCTGAGCTC	TCTCTGGTCA	ATTTTGAGGA	ATCTCAGACG	TTTTTCGGCT	1020
TATATAAGCT	CTAACAGAGAAG	CACTTTGGGA	TTCTTTCCAT	TATGATTCTT	TGTTACAGGC	1080
ACCGGAGAATG	TTGTATTCAAG	TGAGGGTCTT	CTTACATGCA	TTTGAGGTCA	AGTAAGAAGA	1140
CATGAACCAA	GTGGACCTTG	AGACCACAGG	GTTCAAAATG	TCTGTAGCTC	CTCAACTCAC	1200
CTAATGTTA	TGAGCCAGAC	AAATGGAGGA	ATATGACGGA	AGAACATAGA	ACTCTGGGCT	1260
GCCATGTGAA	GAGGGAGAAG	CATGAAAAAG	CAGCTACCCA	GGTGTCTAC	ACTCATCTTA	1320
GTGCCGTGAGA	GTATTTAGGC	AGATTGAAAA	GGACACCTT	TAACTCACCT	CTCAAGGTGG	1380
GCCTTGTAC	CTCAAGGGGG	ACTGTTTTC	AGATACATGG	TTGTGACCTG	AGGATTTAAG	1440
GGATGGAAAA	GGAAGACTAG	AGGCTTGCAT	ATAAAGCTAA	AGAGGCTGAA	AGAGGCCAAT	1500
GCCCCACTGG	CAGCATCTTC	ACTTCTAAAT	GCATATCCTG	AGCCATCGGT	GAAACTAACAA	1560
GATAAGCAAG	AGAGATGTTT	TGGGGACTCA	TTTCATTCT	AACACAGCAT	GTGTATTCTC	1620
AGTGCCAATT	GTAGGGGTGT	GTGTGTGTGT	GTGTGTGTGT	GTGTATGACT	AAAGAGAGAA	1680
TGTAGATATT	GTGAAGTACA	TATTAGGAAA	ATATGGGTG	CATTGGTCA	AGATTTGAA	1740
TGCTTCTGAA	CAATCAACTC	TAATAGTGT	AAAAAATCAT	TGATTGTCAG	CTACTAATGA	1800
TGTTTCTGAA	TAATATAATA	AATATTATG	TAGATGTGCA	TTTTGTGAA	ATGAAAACAT	1860
GTAATAAAAA	GTATATGTTA	GGATACAAAT				1890

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1541 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GGGTGTCTCA	CAGAGAAGCA	AAGAGAAGAG	AACAGGAGAA	ATGGTGTTC	CCTTGACTGC	60
GGAAACTTTA	TAAAGAAAAC	TTAGCTTCTC	TGGAGCAGTC	AGCGTCAGAG	TTCTGTCCTT	120
GACACCTGAG	TCTCCCTCAC	AAGGCTGTGA	GAAGGAAACC	CTTCCCTGGG	GCTGGGTGCC	180
ATGCAGCAGC	CCATGAATT	CCCAGTCCC	CAGATCTTCT	GGGTAGACAG	CAGTGCCACT	240
TCATCTTGGG	CTCCTCCAGG	GTCAGTTTT	CCCTGTCCAT	CTTGTGGGCC	TAGAGGGCCG	300
GACCAAAGGA	GACCGCCACC	TCCACCACCA	CCTGTGTAC	CACTACCACC	GCCATCACAA	360
CCACTCCCAC	TGCCGCCACT	GACCCCTCTA	AAGAAGAAGG	ACCACAAACAC	AAATCTGTGG	420
CTACCGGTGG	TATTTTTCAT	GGTCTGGTG	GCTCTGGTTG	GAATGGGATT	AGGAATGTAT	480
CAGCTCTTCC	ACCTGCAGAA	GGAACTGGCA	GAACCTCCGTG	AGTTCACCAA	CCAAAGCCTT	540
AAAGTATCAT	CTTTGAAAA	GCATAATAGCC	AACCCCCAGTA	CACCCCTCTGA	AAAAAAAGAG	600
CCGAGGAGTG	TGGCCCATT	AACAGGGAAC	CCCCACTCAA	GGTCCATCCC	TCTGGAATGG	660
GAAGACACAT	ATGGAACCGC	TCTGATCTCT	GGAGTGAAGT	ATAAGAAAGG	TGGCCTTGTG	720
ATCAACGAAA	CTGGGTTGTA	CTTCGTGTAT	TCCAAAGTAT	ACTTCCGGGG	TCAGTCTTGC	780
AACAACCAGC	CCCTAAACCA	CAAGGTCTAT	ATGAGGAACT	CTAAGTATCC	TGAGGATCTG	840
GTGCTAATGG	AGGAGAAGAG	GTTGAACCTAC	TGCACTACTG	GCCAGATATG	GGCCCACAGC	900
AGCTACCTGG	GGGCAGTATT	CAATCTTAC	AGTGTGACC	ATTTATATGT	CAACATATCT	960
CAACTCTCTC	TGATCAATT	TGAGGAATCT	AAGACCTTTT	TCGGCTTGTA	TAAGCTTTAA	1020
AAGAAAAGC	ATTTAAAAT	GATCTACTAT	TCTTTATCAT	GGGCACCAGG	AATATTGTCT	1080
TGAATGAGAG	TCTTCTTAAG	ACCTATTGAG	ATTAATTAAG	ACTACATGAG	CCACAAAGAC	1140
CTCATGACCG	CAAGGTCCAA	CAGGTCACT	ATCCTTCATT	TTCTCGAGGT	CCATGGAGTG	1200
GTCCTTAATG	CCTGCATCAT	GAGCCAGATG	GAAGGGAGTC	TGTGACTGAG	GGACATAAAG	1260
CTTTGGGCTG	CTGTGTAGCA	ATGCAGAGGC	ACAGAGAAAG	AACTGTCTGA	TGTTAAATGG	1320
CCAAGAGAAAT	TTAACCAATT	GAAGAAGACA	CCTTACACT	CACTTCCAGG	GTGGGTCTAC	1380
TTACTACCTC	ACAGAGGCCG	TTTTGAGAC	ATAGTTGTGG	TATGAATATA	CAAGGGTGAG	1440
AAAGGAGGCT	CATTTGACTG	ATAAGCTAGA	GACTGAAAAA	AAGACAGTGT	CTCATTGGCA	1500
CCATCTTAC	TGTTACCTGA	TGTTTCTGA	GCCGACCTTT	G		1541

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 888 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GGCTGGTCCC	CTGACAGGTT	GAAGCAAGTA	GACGCCAGG	AGCCCCGGGA	GGGGGCTGCA	60
GTTCCTTCCC	TTCCTTCTCG	GCAGCGCTCC	GCGCCCCCAT	CGCCCCCTCCT	GCGCTAGCGG	120
AGGTGATCGC	CGCGCGATG	CCGGAGGAGG	GTTGGGCTG	CTCGGTGCGG	CGCAGGCCCT	180
ATGGGTGCGT	CCTGCGGCT	GCTTTGGTCC	CATTGGTCGC	GGGCTGGTG	ATCTGCTCG	240
TGGTGTGCAT	CCAGCGCTTC	GCACAGGCTC	AGCAGCAGCT	GCGCTCGAG	TCACTTGGGT	300
GGGACGTAGC	TGAGCTGCAG	CTGAATCACA	CAGGACCTCA	GCAGGACCCC	AGGCTATACT	360
GGCAGGGGGG	CCCAGCACTG	GGCGCTCCT	TCCTGCATGG	ACCAGAGCTG	GACAAGGGC	420
AGCTACGTAT	CCATCGTAT	GGCATCTACA	TGGTACACAT	CCAGGTGACG	CTGGCCATCT	480
GCTCCTCCAC	GACGGCCTCC	AGGCACCACC	CCACCACCT	GGCCGTGGGA	ATCTGCTCTC	540
CCGCCTCCCG	TAGCATCAGC	CTGCTCGTC	TCAGCTTCCA	CCAAGGTTGT	ACCATTGCCT	600
CCCAGCGCTT	GACGCCCTG	GCCCCGAGGGG	ACACACTCTG	CACCAACCTC	ACTGGGACAC	660
TTTTGCCTTC	CCGAAACACT	GATGAGACCT	TCTTGGAGT	GCAGTGGGTG	CGCCCCCTGAC	720
CACTGCTGCT	GATTAGGGTT	TTTTAAATT	TATTTTATT	TATTTAAGTT	CAAGAGAAAA	780
AGTGTACACA	CAGGGGCCAC	CCGGGGTTGG	GGTGGGAGTG	TGGTGGGGGG	TAGTGGTGGC	840
AGGACAAGAG	AAGGCATTGA	GCTTTTCTT	TCATTTCT	ATTA	AAAAAA	888

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1906 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

CCAAGTCACA	TGATTCAAGGA	TTCAGGGGGA	GAATCCTTCT	TGGAACAGAG	ATGGGCCAG	60
AACTGAATCA	GATGAAGAGA	GATAAGGTGT	GATGTGGGGA	AGACTATATA	AAGAATGGAC	120
CCAGGGCTGC	AGCAAGCACT	CAACGGAATG	GCCCCTCCTG	GAGACACAGC	CATGCATGTG	180
CCGGCGGGCT	CCGTGGCCAG	CCACCTGGGG	ACCACGAGCC	GCAGCTATTT	CTATTTGACC	240
ACAGCCACTC	TGGCTCTGTG	CCTTGCTCTC	ACGGTGGCCA	CTATTATGGT	GTTGGTCGTT	300
CAGAGGACGG	ACTCCATTCC	CAACTCACCT	GACAACGTCC	CCCTCAAAGG	AGGAAATTGC	360
TCAGAAGACC	TCTTATGTAT	CCTGAAAAGA	GCTCCATTCA	AGAAGTCATG	GGCCTACCTC	420
CAAGTGGCAA	AGCATCTAAA	CAAAACCAAG	TTGTCCTGGA	ACAAAGATGG	CATTCTCCAT	480
GGAGTCAGAT	ATCAGGATGG	GAATCTGGT	ATCCAATTCC	CTGGTTTGT	CTTCATCATT	540
TGCCAATG	AGTTTCTTGT	ACAATGCCA	AATAATTCTG	TCGATCTGAA	GTTGGAGCTT	600
CTCATCAACA	AGCATATCAA	AAAACAGGCC	CTGGTGACAG	TGTGTGAGTC	TGGAATGCAA	660
ACGAAACACG	TATACCAGAA	TCTCTCTAA	TTCTTGCTGG	ATTACCTGCA	GGTCAACACC	720
ACCATATCAG	TCAATGTGGA	TACATTCCAG	TACATAGATA	CAAGCACCTT	TCCTCTTGAG	780
AATGTGTTGT	CCATCTTCTT	ATACAGTAAT	TCAGACTGAA	CAGTTCTCT	TGGCCTTCAG	840
GAAGAAAGCG	CCTCTCTACC	ATACAGTATT	TCATCCCTCC	AAACACTTGG	GCAAAAGAA	900
AACTTTAGAC	CAAGACAAAC	TACACAGGGT	ATTAATAGT	ATACTCTCC	TTCTGTCTCT	960
TGGAAAGATA	CAGCTCCAGG	GTTAAAAAGA	GAGTTTTAG	TGAAGTATCT	TTCAGATAGC	1020
AGGCAGGGAA	GCAATGTAGT	GTGGTGGGCA	GAGCCCCACA	CAGAACATAGA	AGGGATGAAT	1080
GGATGTCCCCA	GCCCAACCAC	TAATTCACTG	TATGGTCTTG	ATCTATTCT	TCTGTTTGA	1140
GAGCCTCCAG	TTAAAATGGG	GCTTCAGTAC	CAGAGCAGCT	AGCAACTCTG	CCCTAACATGGG	1200
AAATGAAGGG	GAGCTGGGTG	TGAGTGTGTTA	CACTGTGCC	TTCACGGGAT	ACTCTTTTA	1260
TCTGCAGATG	GCCTAATGCT	TAGTTGTCCA	AGTCGCGATC	AAGGACTCTC	TCACACAGGA	1320
AACTCCCTA	TACTGGCAGA	TACACTTGTG	ACTGAACCAT	GCCCCAGTTA	TGCCTGTCTG	1380
ACTGTCACTC	TGGCACTAGG	AGGCTGATCT	TGTACTCCAT	ATGACCCAC	CCCTAGGAAC	1440
CCCCAGGGAA	AACCAGGCTC	GGACAGCCCC	CTGTTCTGGA	GATGGAAAGC	ACAAATTTAA	1500
TACACCACCA	CAATGGAAAA	CAAGTTCAAA	GACTTTACT	TACAGATCCT	GGACAGAAAG	1560
GGCATAATGA	GTCTGAAGGG	CAGTCCTCCT	TCTCCAGGTT	ACATGAGGCA	GGATAAGAA	1620
GTCAGACAGA	GACAGCAAGA	CAGTTAACAA	CGTAGGTAAA	GAAATAGGGT	GTGGTCACTC	1680
TCAATTCACT	GGCAAATGCC	TGAATGGTCT	GTCTGAAGGA	AGCAACAGAG	AAGTGGGAA	1740
TCCAGTCTGC	TAGGCAGGAA	AGATGCCCT	AAGTTCTTGT	CTCTGGCCAG	AGGTGTGGTA	1800
TAGAACCAGA	AACCCATATC	AAGGGTGA	AAGCCCCGCT	TCCGGTATGA	GAAATTAAAC	1860
TTGTATACAA	AATGGTTGCC	AAGGCAACAT	AAAATTATAA	GAATTC		1906

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1619 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

GTCATGGAAT	ACGCCTCTGA	CGCTTCACTG	GACCCCGAAG	CCCCGTGGCC	TCCCGCGCCC	60
CGCGCTCGCG	CCTGCCCGGT	ACTGCCTTGG	GCCCTGGTCG	CGGGGCTGCT	GCTGCTGCTG	120
CTGCTCGCTG	CCGCCTGCGC	CGTCTTCCTC	GCCTGCCCT	GGGCCGTGTC	CGGGGCTCGC	180
GCCTCGCCCC	GCTCCGCGGC	CAGCCCGAGA	CTCCGCGAGG	GTCCCGAGCT	TTCGCCCGAC	240

GATCCCGCCG GCCTCTTGGGA CCTGCGGCAG GGCATGTTTG CGCAGCTGGT GGCCCCAAAT 300
 GTTCTGCTGA TCGATGGGCC CCTGAGCTGG TACAGTGACC CAGGCCTGGC AGGCGTGTCC 360
 CTGACGGGGG GCCTGAGCTA CAAAGAGGAC ACGAAGGAGC TGGTGGTGGC CAAGGCTGGA 420
 GTCTACTATG TCTTCTTCA ACTAGAGCTG CGGCGCGTGG TGGCCGGCGA GGGCTCAGGC 480
 TCCGTTTCAC TTGCGCTGCA CCTGCAGCCA CTGCGCTCTG CTGCTGGGGC CGCOGCCCTG 540
 GCTTTGACCG TGGACCTGCC ACCCGCCCTCC TCCGAGGCTC GGAACTCGGC CTTCGGTTTC 600
 CAGGGCGCT TGCTGCACCT GAGTGCCGGC CAGGCCTGG GCGTCCATCT TCACACTGAG 660
 GCCAGGGCAC GCCATGCCTG GCAGCTTACC CAGGGCGCCA CAGTCTTGGG ACTCTTCCGG 720
 GTGACCCCCG AAATCCCAGC CGGACTCCCT TCACCGAGGT CGGAATAACG CCCAGCCTGG 780
 GTGCAGCCCCA CCTGGACAGA GTCCGAATCC TACTCCATCC TTCATGGAGA CCCCTGGTGC 840
 TGGGTCCCTG CTGCTTCTC TACCTCAAGG GGCTTGGCAG GGGTCCCTGC TGCTGACCTC 900
 CCCTTGAGGA CCCTCCTCAC CCACTCCTTC CCCAAGTTGG ACCTTGATAT TTATTCTGAG 960
 CCTGAGCTCA GATAATATAT TATATATATT ATATATATAT ATATATTCT ATTAAAGAG 1020
 GATCCTGAGT TTGTGAATGG ACTTTTTTAG AGGAGTTGTT TTGGGGGGG GGTCTTCGAC 1080
 ATTGCCGAGG CTGGTCTTGA ACTCCTGGAC TTAGACGATC CTCCTGCCTC AGCCTCCAA 1140
 GCAACTGGGA TTCATCCTT CTATTAATTC ATTGTACTTA TTTGCCTATT TGTGTGTATT 1200
 GAGCATCTGT AATGTGCCAG CATTGTGCC AGGCTAGGGG GCTATAGAAA CATCTAGAAA 1260
 TAGACTGAAA GAAAATCTGA GTTATGGAA TACGTGAGGA ATTTAAAGAC TCATCCCCAG 1320
 CCTCCACCTC CTGTGTGATA CTTGGGGGCT AGCTTTTTTC TTTCTTCTT TTTTTGAGA 1380
 TGGTCTTGT CTGTCAACCA GGCTAGAATG CAGCGGTGCA ATCATGAGTC AATGCAGCCT 1440
 CCAGCCTCGA CCTCCCAGG CTCAGGTGAT CCTCCCATCT CAGCCTCTCG AGTAGCTGGG 1500
 ACCACAGTTG TGTGCCACCA CACTTGGCTA ACTTTTTAAT TTTTTGCGG AGACGGTATT 1560
 GCTATGTTGC CAAGGTTGTT TACATGCCAG TACAATTAT AATAAACACT CATTTTTCC 1619

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1239 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

AGCCTATAAA GCACGGGCAC TGGCGGGAGA CGTGCACTGA CCGACCGTGG TAATGGACCA 60
 GCACACACTT GATGTGGAGG ATACCGCGGA TGCCAGACAT CCAGCAGGTA CTTCGTGCC 120
 CTCGGATGCG GCGCTCCTCA GAGATACCGG GCTCCTCGCG GACGCTGCAGC TCCTCTCAGA 180
 TACTGTGCGC CCCACAAATG CCGCGCTCCC CACGGATGCT GCCTACCCCTG CGGTTAATGT 240
 TCGGGATCGC GAGGCCGCGT GGCGCCCTGC ACTGAACTTC TGTTCCCGCC ACCCAAAGCT 300
 CTATGGCCTA GTCGCTTGG TTTTGCTGCT TCTGATCGCC GCCTGTGTTG CTATCTTCAC 360
 CGCGACCGAG CCTCGGCCAG CGCTCACAAT CACCACCTCG CCCAACCTGG GTACCCGAGA 420
 GAATAATGCA GACCAGGTCA CCCCTGTTTC CCACATTGGC TGCCCCAACAA CTACACAACA 480
 GGGCTCTCCT GTGTCGCCA AGCTACTGGC TAAAAACCAA GCATCGTTGT GCAATACAAC 540
 TCTGAACCTGG CACAGCCAAG ATGGAGCTGG GAGCTCATAC CTATCTCAAG GTCTGAGGTA 600
 CGAAGAAGAC AAAAAGGAGT TGGTGGTAGA CAGTCCCAGG CTCTACTACG TATTTTTGGA 660
 ACTGAAGCTC AGTCCAACAT TCACAAACAC AGGCCACAAG GTGCAGGGCT GGGTCTCTCT 720
 TGTTTGCAA GCAAAGCCTC AGGTAGATGA CTTTGACAAAC TTGGCCCTGA CAGTGGAACT 780
 GTTCCCTTGC TCCATGGAGA ACAAGTTAGT GGACCCTTCC TGGAGTCAAC TGTTGCTCCT 840
 GAAGGCTGGC CACCGCCTCA GTGTGGGTCT GAGGGCTTAT CTGCATGGAG CCCAGGATGC 900
 ATACAGAGAC TGGGAGCTGT CTTATCCCAA CACCACCAAG TTTGGACTCT TTCTTGAA 960
 ACCCGACAAAC CCATGGGAAT GAGAACTATC CTTCTTGTGA CTCCCTAGTTG CTAAGTCCCTC 1020
 AAGCTGCTAT GTTTTATGGG GTCTGAGCAG GGGTCCCTTC CATGACTTTC TCTTGTCTTT 1080
 AACTGGACTT GGTATTTATT CTGAGCATAG CTCAGACAAG ACTTTATATA ATTCACTAGA 1140
 TAGCATTAGT AAACTGCTGG GCAGCTGCTA GATAAAAAAA AATTCTAAA TCAAAGTTA 1200
 TATTTATATT AATATATAAA AATAAAATGTG TTTGTAAAT 1239

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 606 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

ATGATCGAAA	CATAACAACCA	AACTTCTCCC	CGATCTGCGG	CCACTGGACT	GCCCATCAGC	60
ATGAAAATT	TTATGTATTT	ACTTACTGTT	TTTCTTATCA	CCCAGATGAT	TGGGTCA	120
CTTTTGCTG	TGTATCGCTT	CGCACAGGCT	TTTGAATGC	AAAAAGGTGA	TCAGAATCCT	180
CAAATTGCGG	CACATGTCAT	AAAGTGGGCC	AGCAGTAAA	CAACATCTGT	GTTACAGTGG	240
GCTAAAAAG	GATACTACAC	CATGAGCAAC	AACTGGTAA	CCCTGGAAA	TGGGAAACAG	300
CTGACCGTTA	AAAGACAAGG	ACTCTATTAT	ATCTATGCC	AAGTCACCTT	CTGTTCCAAT	360
CGGGAAGCTT	CGAGTCAAGC	TCCATTATA	GCCAGCCTCT	GCCTAAAGTC	CCCCGGTAGA	420
TTCGAGAGAA	TCTTACTCAG	AGCTGCAAAT	ACCCACAGTT	CCGCCAAACC	TTGCGGGCAA	480
CAATCCATT	ACTTGGGAGG	AGTATTGAA	TTGCAACCAG	GTGCTTCGGT	GTTGTCAAT	540
GTGACTGATC	CAAGCCAAGT	GAGCCATGGC	ACTGGCTCA	CGTCCTTGG	CTTACTCAA	600
CTCTGA						606

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 783 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

ATGATCGAAA	CATAACAACCA	AACTTCTCCC	CGATCTGCGG	CCACTGGACT	GCCCATCAGC	60
ATGAAAATT	TTATGTATTT	ACTTACTGTT	TTTCTTATCA	CCCAGATGAT	TGGGTCA	120
CTTTTGCTG	TGTATCTTCA	TAGAAGATTG	GATAAGGTG	AAGAGGAAGT	AAACCTTCAT	180
GAAGATTTG	TATTCTAAA	AAAGCTAAAG	AGATGCAACA	AAGGAGAAGG	ATCTTTATCC	240
TTGCTGA	ACT GTGAGGAGAT	GAGAAGGCAA	TTTGAAGACC	TTGTCAAGGA	TATAACGTTA	300
AACAAAGAAG	AGAAAAAGA	AAACAGCTT	GAAATGCAA	AAGGTGATCA	GAATCCTCAA	360
ATTGCGGCAC	ATGTCATAAG	TGAGGCCAGC	AGTAAAACAA	CATCTGTGTT	ACAGTGGGCT	420
GAAGAAAGGAT	ACTACACCAT	GAGCAACAAC	TTGGTAACCC	TGGAAATGG	GAACAGCTG	480
ACCGTTAAA	GACAAGGACT	CTATTATATC	TATGCCAAG	TCACCTTCTG	TTCCAATCGG	540
GAAGCTTCGA	GTCAAGCTCC	ATTATAGCC	AGCCTCTGCC	TAAAGTCCCC	CGGTAGATT	600
GAGAGAATCT	TACTCAGAGC	TGCAAATACC	CACAGTTCCG	CCAAACCTTG	CGGGCAACAA	660
TCCATTCACT	TGGGAGGAGT	ATTGAATTG	CAACCAGGTG	CTTCGGTGT	TGTCAATGTG	720
ACTGATCAA	GCCAAGTGAG	CCATGGCACT	GGCTTCACGT	CCTTGGCTT	ACTCAAAC	780
TGA						783

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 558 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

CTGCTGCACT	TCGGGGTAAT	CGGCCCCAG	AGGAAGAGC	AGTCCCCAGG	TGGCCCCCTCC	60
ATCAACAGCC	CTCTGGTTCA	AACACTCAGG	TCCTCTTCTC	AAGCCTCAAG	TAACAAGCCG	120
GTAGCCCACG	TTGTAGCCGA	CATCAACTCT	CCGGGGCAGC	TCCGGTGGTG	GGACTCGTAT	180
GCCAATGCC	TCATGGCAA	CGGTGTGAAG	CTGAAAGACA	ACCAGCTGGT	GGTGCCTGCT	240
GACGGGCTTT	ACCTCATCTA	CTCACAGGTC	CTCTTCAGGG	GCCAAGGCTG	CCCTTCCACC	300
CCCTTGTTC	TCACCCACAC	CATCAGCCGC	ATTGCAGTCT	CCTACCAGAC	CAAGGTCAAC	360
ATCCTGTCTG	CCATCAAGAG	CCCTTGCCAC	AGGGAGACCC	CAGAGTGGC	TGAGGCCAAG	420
CCCTGGTACG	AACCCATCTA	CCAGGGAGGA	GTCTTCCAGC	TGGAGAAGGG	AGATCGCCTC	480
AGTGCTGAGA	TCAACCTGCC	GGACTACCTG	GACTATGCCG	AGTCCGGCA	GGTCTACTTT	540
GGGATCATTG	CCCTGTGA					558

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	1783 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

CAAGTCACAT	GATCCAGGAT	GCAGGGAAA	ATCCTTCTTG	GAACAGAGCT	GGGTACAGAA	60
CCGAATCAGA	TGAGGAGAGA	TAAGGTGTGA	TGTGGGACAG	ACTATATAAA	GCATGGAGCC	120
AGGGCTGCAA	CAAGCAGGCA	GCTGTGGGGC	TCCTTCCCCT	GACCCAGCCA	TGCAGGTGCA	180
GCCCCGCTCG	GTAGCCAGCC	CCTGGAGAAG	CACGAGGCC	TGGAGAAGCA	CAAGTCGCAG	240
CTACTTCTAC	CTCAGCACCA	CCGCACTGGT	GTGCCCTGTT	GTGGCAGTGG	CGATCATTCT	300
GGTACTGGTA	GTCCAGAAAA	AGGACTCCAC	TCCAAATACA	ACTGAGAAGG	CCCCCCTTAA	360
AGGAGGAAAT	TGCTCAGAGG	ATCTCTTCTG	TACCCCTGAAA	AGTACTCCAT	CCAAGAACGT	420
ATGGGCCTAC	CTCCAAGTGT	CAAAGCATCT	CAACAATACC	AAACTGTCA	GGAACGAAGA	480
TGGCACCATC	CACGGACTCA	TATACCAGGA	CGGGAACCTG	ATAGTCCAAT	TCCCTGGCTT	540
GTACTTCATC	GTTTGCACAC	TGCAGTTCT	CGTGCAGTGC	TCAAATCATT	CTGTGGACCT	600
GACATTGCGAG	CTCCTCATCA	ATTCCAAGAT	CAAAAAGCAG	ACGTTGGTAA	CAGTGTGTGA	660
GTCTGGAGTT	CAGAGTAAGA	ACATCTACCA	GAATCTCT	CAGTTTTGC	TGCATTACTT	720
ACAGGTCAAC	TCTACCATAT	CAGTCAGGGT	GGATAATTTC	CAGTATGTGG	ATACAAACAC	780
TTTCCCTCTT	GATAATGTGC	TATCCGTCTT	CTTATATAGT	AGCTCAGACT	GAATAGTTGT	840
TCTTAACCTT	TATGAAAATG	CTGTCACCA	TACAGTACTT	CATCTGTCCA	AAACATGGGCC	900
AAAGAAAATA	TTAGGACAAC	TCAAACTAAG	CATGTGAGTT	AGTGCACCTTC	TCTTCTGTC	960
CTTTGGAAAAA	ATACAAACCC	AGGATTAGA	AAGTGGAGTC	TCCTTCAGAT	GCACAAACAG	1020
GAAAAGATGT	GATATGTGCA	CAGAGACCTA	CTTGGGACT	AGAAGGGGTG	TGAGTTGTCC	1080
CAGTATAACC	ACTAATTACAC	TGACCTTGAG	CCATTTTTC	TTCCCCCTGG	AACTTGGGGT	1140
CTGAATCTGG	AAAAGTAGGA	GATGAGATT	ACATTTCCC	AATATTTCT	TCAACTCAGA	1200
AGACGAGACT	GTGGAGCTGA	GCTCCCTACA	CAGATGAAGG	CCTCCCATGG	CATGAGGAAA	1260
ATGATGGTAC	CAGTAATGTC	TGTCTGACTG	TCATCTCAGC	AAGTCCTAAG	GACTTCCATG	1320
CTGCTTGTGTT	GAAAGATACT	CTAACCTCTT	GTAATGGCA	AAGTGATCCT	GTCTCTCACT	1380
GAGGGGAGTA	GCTGCTGCCA	TCTCCTGAGA	CATACATGGA	GACATTTCT	GCCCAAATT	1440
CATTCTGTGT	GCAGTTTTA	AGTATTCCCC	CAAAAGTTCT	TGACAATGAG	AACTTTGAAT	1500
GTGGGAAGAG	CTTCTGGACA	GCAAACATTA	ACAGCTTCTC	CTGACCAAGAG	AGACCATGCA	1560
AGCTTGGTCT	TAGACCCATC	AAGCTTGAGG	TTTCTACATT	GTGGGAGACA	GACTTTGAC	1620
AAACCATTG	AGTTGATGTC	TGGGCCCTG	GGAGTTCTCC	TTCAGTAAGG	AGAGCAAGCC	1680
GTTCTAGTGC	TGTGTAGAG	GATGGAGTAA	AATAGACACT	TTTCTGAAGG	AAAGGAGAAC	1740
AAAGTTCCAG	AAAAAGGCTA	GAAAATGTTT	AAAAAGAAAAA	AAA		1783

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1047 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

AGAGAGCGCT	GGGAGCCGGA	GGGGAGCGCA	GCGAGTTTG	GCCAGTGGTC	GTGCAGTCCA	60
AGGGGCTGGA	TGGCATGCTG	GACCCAAGCT	CAGCTCAGCG	TCCGGACCCA	ATAACAGTT	120
TACCAAGGGA	GCAGCTTCT	ATCCTGGCCA	CACTGAGGTG	CATAGCGTAA	TGTCATGTT	180
GTTCTACACT	CTGATCACAG	CTTTTCTGAT	CGGCATACAG	GCGGAACAC	ACTCAGAGAG	240
CAATGTCCCT	GCAGGACACA	CCATCCCCCA	AGTCCACTGG	ACTAAACTTC	AGCATTCCCT	300
TGACACTGCC	CTTCGCAGAG	CCCAGCAGCG	CCCAGCAGCG	GCGATAGCTG	CACCGCGTGGC	360
GGGGCAGACC	CGCAACATTA	CTGTGGACCC	CAGGCTGTTT	AAAAAGCGGC	GACTCCGTTTC	420
ACCCCGTGTG	CTGTTAGCA	CCCAGCCTCC	CCGTGAAGCT	GCAGACACTC	AGGATCTGGA	480
CTTCGAGGTC	GGTGGTGCTG	CCCCCTCAA	CAGGACTCAC	AGGAGCAAGC	GGTCATCATC	540
CCATCCCAC	TTCCACAGGG	GCGAATTCTC	GGTGTGTGAC	AGTGTCAAGC	TGTGGGTTGG	600
GGATAAGACC	ACCGCCACAG	ACATCAAGGG	CAAGGAGGTG	ATGGTGTG	GAGAGGTGAA	660
CATTAACAAAC	AGTGTATTCA	AACAGTACTT	TTTGAGACC	AAGTGC	ACCCAAATCC	720
CGTTGACAGC	GGGTGCCGGG	GCATTGACTC	AAAGCACTGG	AACTCATATT	GTACCAACGAC	780
TCACACCTT	GTCAAGGC	TGACCATGGA	TGGCAAGCAG	GCTGCCTGGC	GGTTTATCCG	840
GATAGATACG	GCCTGTGTG	GTGTGCTCAG	CAGGAAGGCT	GTGAGAAAGAG	CCTGACCTGC	900
CGACACGCTC	CCTCCCCCTG	CCCCCTCTAC	ACTCTCCTGG	GCCCCCTCCCT	ACCTCAACCT	960
GTAAATTATT	TTAAATTATA	AGGACTGCAT	GGTAATTAT	AGTTTATACA	GTTTAAAGA	1020
ATCATTATTT	ATTAATT	TGGAAGC				1047

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1176 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GAGCGCTGG	AGCCGGAGGG	GAGCGCATCG	AGTGACTTTG	GAGCTGGCCT	TATATTGGA	60
TCTCCGGGC	AGCTTTTGG	AAACTCCTAG	TGAACATGCT	GTGCCTCAAG	CCAGTGAAAT	120
TAGGCTCCCT	GGAGGTGGGA	CACGGGCAGC	ATGGTGGAGT	TTTGGCCTGT	GGTCGTGCAG	180
TCCAGGGGGC	TGGATGGCAT	GCTGGACCA	AGCTCACCTC	AGTGTCTGGG	CCCAATAAAG	240
GTTTTGCCAA	GGACCGAGCT	TTCTATAC	GCCGCAGTGA	GGTGCATAGC	GTAATGTCCA	300
TGTTGTTCTA	CACTCTGATC	ACTGGCTTT	TGATCGGCGT	ACAGGCAGAA	CCGTACACAG	360
ATAGCAATGT	CCCAGAAGGA	GACTCTGTCC	CTGAAGCCCA	CTGGACTAAA	CTTCAGCATT	420
CCCTTGACAC	AGCCCTCCGC	AGAGCCCGCA	GTGCCCCCTAC	TGCACCAATA	GCTGCCCGAG	480
TGACAGGGCA	GACCCGCAAC	ATCACTGTAG	ACCCCAGACT	GTAAAGAAA	CGGAGACTCC	540
ACTCACCCCG	TGTGCTGTT	AGCACCCAGC	CTCCACCCAC	CTCTTCAGAC	ACTCTGGATC	600
TAGACTTCCA	GGCCCATGGT	ACAATCCCTT	TCAACAGGAC	TCACCGGAGC	AAGCGCTCAT	660
CCACCCACCC	AGTCTTCCAC	ATGGGGGAGT	TCTCAGTGTG	TGACAGTGT	AGTGTGTGGG	720
TTGGAGATAA	GACCACAGCC	ACAGACATCA	AGGGCAAGGA	GGTGACAGTG	CTGGCCGAGG	780
TGAACATTAA	CAACAGTGT	TTCAGACAGT	ACTTTTTG	GACCAAGTG	CGAGCCTCCA	840
ATCCTGTTGA	GAGTGGGTGC	CGGGGCATCG	ACTCCAAACA	CTGGAAC	TACTGCACCA	900
CGACTCACAC	CTTCGTCAAG	GC GTTGACAA	CAGATGAGAA	GCAGGCTGCC	TGGAGGTTCA	960
TCCGGATAGA	CACAGCCTGT	GTGTGTGTG	TCAGCAGGAA	GGCTACAAGA	AGAGGCTGAC	1020

TTGCCTGCAG	CCCCCTTCCC	CACCTGCC	CTCCACACTC	TCTTGGGCC	CTCCCTACCT	1080
CAGCCTGTA	ATTATTTAA	ATTATAAGGA	CTGCATGATA	ATTTATCGTT	TATACAATTT	1140
TAAAGACATT	ATTTATTAAA	TTTC	AAAGC	ATCCTG		1176

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1623 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

TCAGAGTCCT	GTCCTTGACA	CTTCAGTCTC	CACAAGACTG	AGAGGAGGAA	ACCCTTCCT	60
GGGGCTGGGT	GCCATGCAGC	AGCCCGTGAA	TTACCCATGT	CCCCAGATCT	ACTGGGTAGA	120
CAGCAGTGCC	ACTTCTCCTT	GGGCTCCTCC	AGGGTCAGTT	TTTTCTTGTC	CATCCTCTGG	180
GCCTAGAGGG	CCAGGACAAA	GGAGACCACC	GCCTCCACCA	CCACCTCCAT	CACCACTACC	240
ACCGCCTTC	CAACCACCCC	CGCTGCCTCC	ACTAACGCCCT	CTAAAGAAGA	AGGACAACAT	300
AGAGCTGTGG	CTACCGGTGA	TATTTTCAT	GGTGCTGGTG	GCTCTGGTTG	GAATGGGGTT	360
AGGAATGTAT	CAACTCTTTC	ATCTACAGAA	GGAACTGGCA	GAACCTCGTG	AGTTCACCAA	420
CCACAGCCTT	AGAGTATCAT	CTTTTGAAAA	GCAAATAGCC	AACCCCAGCA	CACCTCTGA	480
AACCAAAAAG	CCAAGGGAGTG	TGGCCCACCTT	AACAGGGAAC	CCCCGCTCAA	GGTCCATCCC	540
TCTGGAATGG	GAAGACACAT	ATGGAACTGC	TTTGATCTCT	GGAGTGAAGT	ATAAGAAAGG	600
CGGCCTTGTG	ATCAATGAGG	CTGGGTTGTA	CTTCGTATAT	TCCAAAGTAT	ACTTCCGGGG	660
TCAGTCTTGC	AACAGCCAGC	CCCTAAGCCA	CAAGGTCTAT	ATGAGGAACT	TTAAGTATCC	720
TGGGGATCTG	GTGCTAATGG	AGGAGAAGAA	GTTGAATTAC	TGCACTACTG	GCCAGATATG	780
GGCCCACAGC	AGCTACCTAG	GGGCAGTATT	TAATCTTACC	GTTGCTGACC	ATTATATATGT	840
CAACATATCT	CAACTCTCTC	TGATCAATT	TGAGGAATCT	AAGACCTTTT	TTGGCTTATA	900
TAAGCTTTAA	AGGAAAAGC	ATTTAGAAT	GATCTATTAT	TCTTATCAT	GGATGCCAGG	960
ATATTTGTCT	TCAATGAGAG	TCTTCTTAAG	ACCAATTGAG	CCACAAAGAC	CACAAGGTCC	1020
AACAGGTCA	CTACCCCTCA	TTTTCTAGAG	GTCCATGGAG	TGGTCCTTAA	TGCCTGCATC	1080
ATGAGCCAGA	TGGGAAGAAG	ACTGTTCTG	AGGAACATAA	AGTTTTGGC	TGCTGTGTGG	1140
CAATGCAGAG	GCAAAGAGAA	GGAACTGTCT	GATGTTAAAT	GGCCAAGAGC	ATTTTAGCCA	1200
TTGAAGAAAA	AAAAAAACCTT	TAAACTCACC	TTCCAGGGTG	GGTCTACTTG	CTACCTCACA	1260
GGAGGCCGTC	TTTTAGACAC	ATGGTTGTGG	TATGACTATA	CAAGGGTGAG	AAAGGATGCT	1320
AGGTTTCATG	GATAAGCTAG	AGACTGAAAA	AAGCCAGTGT	CCCATTGGCA	TCATCTTAT	1380
TTTTAAGTGA	TGTTTCTGA	GCCCACCTT	GATGCTAAC	GAGAAATAAG	AGGGGTGTTT	1440
GAGGCACAAAG	TCATTCTCTA	CATAGCATGT	GTACCTCCAG	TGCAATGATG	TCTGTGTGTG	1500
TTTTTATGTA	TGAGAGTAGA	GCGATTCTAA	AGAGTCACAT	GAGTACAACG	CGTACATTAC	1560
GGAGTACATA	TTAGAACACGT	ATGTGTTACA	TTTGATGCTA	GAATATCTGA	ATGTTCTTG	1620
CTA						1623

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GTAAAGCTTT TCAGTCAGCA TGATAGAA

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GTTTCTAGAT CAGAGTTGA GTAAGCC

27

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

CCAAGACTAG TTAACACAGC ATGATCGAAA

30

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

CCAATGCGGC CGCACTCAGA ATTCAACCTG

30

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 972 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

TCTAGACTCA GGACTGAGAA GAAGTAAAAC CGTTTGCTGG GGCTGGCCTG ACTCACCAAGC
TGCCATGCAG CAGCCCTTCA ATTACCCATA TCCCCAGATC TACTGGGTGG ACAGCAGTGC
CAGCTCTCCC TGGGCCCTCTC CAGGCACAGT TCTTCCCTGT CCAACCTCTG TGCCCGAGAAG

60

120

180

GCCTGGTCAA	AGGAGGCCAC	CACCACCACC	GCCACCGCCA	CCACTACCAC	CTCCGCCGCC	240
GCCGCCACCA	CTGCCTCCAC	TACCGCTGCC	ACCCCTGAAG	AAGAGAGGGA	ACCACAGCAC	300
AGGCCTGTGT	CTCCTTGTA	TGTTTTTCAT	GGTTCTGGTT	GCCTTGGTAG	GATTGGGCCT	360
GGGGATGTTT	CAGCTCTTCC	ACCTACAGAA	GGAGCTGGCA	GAACCTCCGAG	AGTCTACCAG	420
CCAGATGCAC	ACAGCATCAT	CTTGGAGAA	GCAAATAGGC	CACCCCAGTC	CACCCCTGA	480
AAAAAAGGAG	CTGAGGAAAG	TGGCCCATT	AACAGGCAAG	TCCAACCTCAA	GGTCATGCC	540
TCTGGAATGG	GAAGACACCT	ATGGAATTGT	CCTGCTTTCT	GGAGTGAAGT	ATAAGAAGGG	600
TGGCCTTGTG	ATCAATGAAA	CTGGGCTGTA	CTTTGTATAT	TCCAAAGTAT	ACTTCCGGGG	660
TCAATCTTGC	AACAACCTGC	CCCTGAGCCA	CAAGGTCTAC	ATGAGGAACT	CTAAGTATCC	720
CCAGGATCTG	GTGATGATGG	AGGGGAAGAT	GATGAGCTAC	TGCACTACTG	GGCAGATGTG	780
GGCCCGCAGC	AGCTACCTGG	GGGCAGTGT	CAATCTTACC	AGTGCTGATC	ATTATATATGT	840
CAACGTATCT	GAGCTCTCTC	TGGTCAATT	TGAGGAATCT	CAGACGTTT	TCGGCTTATA	900
TAAGCTCTAA	GAGAACACT	TTGGGATTCT	TTCCATTATG	ATTCTTTGTT	ACAGGCACCG	960
AGATGTTCTA	GA					972

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 885 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

ATGCAGCAGC	CCATGAATTA	CCCATGTC	CAGATCTTCT	GGGTAGACAG	CAGTGC	60
TCATCTGGG	CTCCTCCAGG	GTCAGTTTT	CCCTGTCCAT	CTTGTGGGCC	TAGAGGGCCG	120
GACCAAAGGA	GACCGCCACC	TCCACCACCA	CCTGTGTCAC	CACTACCACC	GCCATCACAA	180
CCACTCCCAC	TGCCGCCACT	GACCCCTCTA	AAGAAGAAGG	ACCACAAACAC	AAATCTGTGG	240
CTACCGGTGG	TATTTTCAT	GGTTCTGGTG	GCTCTGGTTG	GAATGGGATT	AGGAATGTAT	300
CAGCTCTTCC	ACCTGCAGAA	GGAACTGGCA	GAAC	AGTCACCAA	CCAAAGCCTT	360
AAAGTATCAT	CTTTGAAAAA	GCAAATAGCC	AACCC	CACCC	AAAAAAAGAG	420
CCGAGGAGTG	TGGCCCATT	AA	GGTCC	GGTCCATCCC	TCTGGAATGG	480
GAAGACACAT	ATGAAACGC	TCTGATCTC	GGAGTGAAGT	ATAAGAAAGG	TGGCCTTGTG	540
ATCAACGAAG	CTGGGTTGTA	CTTCGTATAT	TCCAAAGTAT	ACTTCCGGGG	TCAGTCTTGC	600
AACAACCAGC	CCCTAAACCA	CAAGGTCTAT	ATGAGGAACT	CTAAGTATCC	TGGGGATCTG	660
GTGCTAATGG	AGGAGAAGAG	GTTGA	TGCACTACTG	GACAGATATG	GGCCACAGC	720
AGCTACCTGG	GGGCAGTATT	CAATCTTACC	AGTGCTGACC	ATTATATATGT	CAACATATCT	780
CAACTCTCTC	TGATCAATT	TGAGGAATCT	AAGACCTTT	TCGGCTTGT	TAAGCTTAA	840
AAGAAAAAGC	ATTTAAAAT	GATCTACTAT	TCTTATCAT	GGCA		885

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

CTTAAGCTTC TACAGGACTG AGAAGAAGT

29

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

CTTGAATTCC AACATTCTCG GTGCCTGTAA

30

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

TCAGGATCCA CAAGGCTGTG AGAAGGA

27

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

CTTGTCTAGA CCTGGTGCCC ATGATA

26

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 680 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

ATGCCGGAGG AAGGTCGCC	TTGCCCTGG GTTCGCTGGA	GCGGGACCGC GTTCCAGCGC	60
CAATGGCCAT GGCTGCTGCT	GGTGGTGTGTT ATTACTGTGT	TTTGCTGTTG GTTTCATTGT	120
AGCGGACTAC TCAGTAAGCA	GCAACAGAGG CTGCTGGAGC	ACCCTGAGCC GCACACAGCT	180
GAGTTACAGC TGAATCTCAC	AGTTCCTCGG AAGGACCCC	CACTGCGCTG GGGAGCAGGC	240
CCAGCCTTGG GAAGGTCCCT	CACACACGGA CCAGAGCTGG	AGGAGGGCCA TCTGCGTATC	300
CATCAAGATG GCCTCTACAG	GCTGCATATC CAGGTGACAC	TGGCCAAC TGCTTCCCCA	360
GGCAGCACCC TGCAGCACAG	GGCCACCCTG GCTGTGGCA	TCTGCTCCCC CGCTGCGCAC	420
GGCATCAGCT TGCTGCGTGG	GCGCTTGGG CAGGACTGTA	CAGTGGCATT ACAGCGCCTG	480
ACATACCTGG TCCACGGAGA	TGTCCTCTGT ACCAACCTCA	CCCTGCCTCT GCTGCCGTCC	540
CGCAACGCTG ATGAGACCTT	CTTGGAGTT CAGTGGATAT	GCCCTTGACC ACAACTCCAG	600
GATGACTTGT GAATATTTT	TTTCTTTCA AGTTCTACGT	ATTTATAAAAT GTATATAGTA	660
CACATAAAAA AAAA			680

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 846 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

ATGCAGCAGC CCTTCAATTA CCCATATCCC CAGATCTACT	GGGTGGACAG CAGTGCCAGC	60
TCTCCCTGGG CCCCTCCAGG CACAGTTCTT CCCTGTCAA	CCTCTGTGCC CAGAAGGCCT	120
GGTCAAAGGA GGCCACCAACC ACCACCGCCA CCGCCACCA	TACCACCTCC GCCGCCGCC	180
CCACCACTGC CTCCACTACC GCTGCCACCC	CTGAAGAAGA GAGGGAACCA	240
CTGTGTCTCC TTGTGATGTT TTTCATGGTT CTGGTTGCCT	TGGTAGGATT GGGCCTGGGG	300
ATGTTTCAGC TCTTCACCT GCAGAAGGAA	CTGGCAGAAC TCCGTGAGTT	360
AGCCTTAAAG TATCATCTTT TGAAAAGCAA	ATAGGCCACC CCAGTCCACC	420
AAGGAGCTGA GGAAAGTGGC	CCATTTAACAA GGCAAGTCCA	480
GAATGGGAAG ACACCTATGG	ACTCAAGGTC CATGCCTCTG	540
CTTGTGATCA ATGAAACTGG	TGAAAGTATAA GAAGGGTGGC	600
TCTTGCACAA ACCTGCCCT	GAGCCACAAAG GTCTACATGA	660
GATCTGGTGA TGATGGAGGG	GGAACTCTAA GTATCCCCAG	720
CGCAGCAGCT ACCTGGGGGC	AGTGTCAAT CTTACCAGTG	780
GTATCTGAGC TCTCTCTGGT	CTGATCATT ATATGTCAAC	840
CAATTTGAG	CGTTTTCGG CTTATATAAG	846
CTCTAA		

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 786 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

ATGCAGCAGC CCTTCAATTA CCCATATCCC CAGATCTACT GGGTGGACAG CAGTGCCAGC	60
TCTCCCTGGG CCCCTCCAGG CACAGTTCTT CCCTGTCCAA CCTCTGTGCC CAGAAGGCCT	120
GGTCAAAGGA GGCCACCACC ACCACCGCCA CGGCCACCAC TACCACCTCC GCCGCCGCCG	180
CCACCACTGC CTCCACTACC GCTGCCACCC CTGAAGAAGA GAGGGAACCA CAGCACAGGC	240
CTGTGTCTCC TTGTGATGTT TTTCATGGTT CTGGTTGCCT TGGTAGGATT GGGCCTGGGG	300
ATGTTTCAGC TCTTCCGCTT CGCACAGGCT ATAGGCCACC CCAGTCCACC CCCTGAAAAA	360
AAGGAGCTGA GGAAAGTGGC CCATTTAACCA GGCAAGTCCA ACTCAAGGTC CATGCCCTTG	420
GAATGGGAAG ACACCTATGG ATTGTCTTG CTTCTGGAG TGAAGTATAA GAAGGGTGGC	480
CTTGTGATCA ATGAAACTGG GCTGTACTTT GTATATTCCA AAGTATACTT CCGGGGTCAA	540
TCTTGCACACA ACCTGCCCT GAGCCACAAAG GTCTACATGA GGAACCTAA GTATCCCCAG	600
GATCTGGTGA TGATGGAGGG GAAGATGATG AGCTACTGCA CTACTGGGCA GATGTGGGCC	660
CGCAGCAGCT ACCTGGGGGC AGTGTCAAT CTTACCAGTG CTGATCATT ATATGTCAAC	720
GTATCTGAGC TCTCTCTGGT CAATTTGAG GAATCTCAGA CGTTTTCGG CTTATATAAG	780
CTCTAA	786

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 864 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

ATGCAGCAGC CCTTCAATTA CCCATATCCC CAGATCTACT GGGTGGACAG CAGTGCCAGC	60
TCTCCCTGGG CCCCTCCAGG CACAGTTCTT CCCTGTCCAA CCTCTGTGCC CAGAAGGCCT	120
GGTCAAAGGA GGCCACCACC ACCACCGCCA CGGCCACCAC TACCACCTCC GCCGCCGCCG	180
CCACCACTGC CTCCACTACC GCTGCCACCC CTGAAGAAGA GAGGGAACCA CAGCACAGGC	240
CTGTGTCTCC TTGTGATGTT TTTCATGGTT CTGGTTGCCT TGGTAGGATT GGGCCTGGGG	300
ATGTTTCAGC TCTTCCAATC CTCCATCCCTC CCCTATGCCG GAGGAGGGTT CGGGCTGCTC	360
GGTGGCGCGC AGGCCCTATG GGTGCGTCCT CGGGCCATCC TCAATCCTAT AGGCCACCCC	420
AGTCCACCCCC CTGAAAAAAA GGAGCTGAGG AAAGTGGCCC ATTAAACAGG CAAGTCCAAC	480
TCAAGGTCCA TGCCTCTGGA ATGGGAAGAC ACCTATGGAA TTGTCTGCT TTCTGGAGTG	540
AAGTATAAGA AGGGTGGCCT TGTGATCAAT GAAACTGGGC TGTACTTTGT ATATTCCAAA	600
GTATACTTCG GGGGTCAATC TTGCAACAAAC CTGCCCCCTGA GCCACAAGGT CTACATGAGG	660
AACTCTAAGT ATCCCCAGGA TCTGGTGTGAG ATGGAGGGGA AGATGATGAG CTACTGCACT	720
ACTGGGCAGA TGTGGGCCCG CAGCAGCTAC CTGGGGCAG TGTCAATCT TACCAAGTGT	780
GATCATTAT ATGTCAACGT ATCTGAGCTC TCTCTGGTCA ATTTTGAGGA ATCTCAGACG	840
TTTTTCGGCT TATATAAGCT CTAA	864

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 828 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

ATGCAGCAGC CCTTCAATT	CCCATATCCC CAGATCTACT	GGGTGGACAG CAGTGCCAGC	60
TCTCCCTGGG CCCCTCCAGG	CACAGTTCTT CCCTGTCCAA	CCTCTGTGCC CAGAAGGCCT	120
GGTCAAAGGA GGCCACCACC	ACCACCGCCA CCGCCACCAC	TACCACCTCC GCCGCCGCCG	180
CCACCACTGC CTCCACTACC	GCTGCCACCC CTGAAGAAGA	GAGGGAACCA CAGCACAGGC	240
CTGTGTCTCC TTGTGATGTT	TTTCATGGTT CTGGTTGCCT	TGGTAGGATT GGGCCTGGGG	300
ATGTTTCAGC TCTTCCACCT	ACAGCGAGAG TCTACCAGCC	AGATGCACAC AGCATCATCT	360
TTGGAGAACG AAATAGGCCA	CCCCAGTCCA CCCCCCTGAAA	AAAAGGAGCT GAGGAAAGTG	420
GCCCATTAA CAGGCAAGTC	CAACTCAAGG TCCATGCCTC	TGGAATGGGA AGACACCTAT	480
GGAATTGTCC TGCTTCTGG	AGTGAAGTAT AAGAAGGGTG	GCCTTGTGAT CAATGAAACT	540
GGGCTGTACT TTGTATATTC	CAAAGTATAC TTCCGGGGTC	AATCTTGCAA CAACCTGCC	600
CTGAGCCACA AGGTCTACAT	GAGGAACTCT AAGTATCCCC	AGGATCTGGT GATGATGGAG	660
GGGAAGATGA TGAGCTACTG	CACTACTGGG CAGATGTGGG	CCCGCAGCAG CTACCTGGGG	720
GCAGTGTCA ATCTTACCA	TGCTGATCAT TTATATGTCA	ACGTATCTGA GCTCTCTCTG	780
GTCATTTCG AGGAATCTCA	GACGTTTTTC GGCTTATATA	AGCTCTAA	828

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 846 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

ATGGCTATGA TGGAGGTCCA GGGGGGACCC AGCCTGGGAC	AGACCTGCGT GCTGATCGTG	60
ATCTTCACAG TGCTCCTGCA GTCTCTCTGT	GTGGCTGTAA CTTACGTGTA CTTTACCAAC	120
GAGCTGAAGC AGATGCAGGA CAAGTACTCC	AAAAGTGGCA TTGCTTGTGTT CTTAAAAGAA	180
GATGACAGTT ATTGGGACCC CAATGACGAA GAGAGTATGA	ACAGCCCCCTG CTGGCAAGTC	240
AAAGTGGCAAC TCCGTCACT CGTTAGAAAAG ATGATTTGA	GAACCTCTGA GGAAACCATT	300
TCTACAGTTC AAGAAAAGCA ACAAAATATT	TCTCCCTAG TGAGAGAAAG AGGTCTCAG	360
AGAGTAGCAG CTCACATAAC TGGGACCAGA GGAAGAAGCA	ACACATTGTC TTCTCCAAAC	420
TCCAAGAATG AAAAGGCTCT GGGCCGCAAA ATAAACTCCT	GGGAATCATC AAGGAGTGGG	480
CATTCAATTCC TGAGCAACTT GCACCTGAGG AATGGTGAAC	TGGTCATCCA TGAAAAAGGG	540
TTTTACTACA TCTATTCCCA AACATACTTT CGATTTCAGG	AGGAAATAAA AGAAAACACA	600
AAGAACGACA AACAAATGGT CCAATATATT TACAAATACA	CAAGTTATCC TGACCCCTATA	660
TTGTTGATGA AAAGTGCTAG AAATAGTTGT TGGCTAAAG	ATGCAGAATA TGGACTCTAT	720
TCCATCTATC AAGGGGAAT ATTTGAGCTT AAGGAAAATG	ACAGAATTTC TGTTCTGT	780
ACAAATGAGC ACTTGATAGA CATGGACCAT GAAGCCAGTT	TTTCGGGGC CTTTTAGTT	840
GGCTAA		846

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 876 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

ATGCCTTCCT CAGGGGCCCT GAAGGACCTC AGCTTCAGTC AGCACTTCAG GATGATGGTG 60
ATTTCATAG TGCTCTGCA GGTGCTCCTG CAGGCTGTGT CTGTGGCTGT GACTTACATG 120
TACTTCACCA ACGAGATGAA GCAGCTGCAG GACAATTACT CCAAATTGG ACTAGCTTGC 180
TTCTCAAAGA CGGATGAGGA TTTCTGGAC TCCACTGATG GAGAGATCTT GAACAGACCC 240
TGCTTGCAGG TTAAGAGGCA ACTGTATCAG CTCATTGAAG AGGTGACTTT GAGAACCTTT 300
CAGGACACCA TTTCTACAGT TCCAGAAAAG CAGCTAAGTA CTCCTCCCTT GCCCAGAGGT 360
GGAAGACCTC AGAAAGTGGC AGCTCACATT ACTGGGATCA CTCGGAGAAG CAACTCAGCT 420
TTAATTCCAA TCTCCAAGGA TGGAAAGACC TTAGGCCAGA AGATTGAATC CTGGGAGTCC 480
TCTCGGAAAG GGCATTTCATT TCTCAACCAC GTGCTCTTTA GGAATGGAGA GCTGGTCATC 540
GAGCAGGAGG GCCTGTATTA CATCTATTCC CAAACATACT TCCGATTCA GGAAGCTGAA 600
GACGCTTCCA AGATGGTCTC AAAGGACAAG GTGAGAACCA AACAGCTGGT GCAGTACATC 660
TACAAGTACA CCAGCTATCC GGATCCCATA GTGCTCATGA AGAGCGCCAG AAACAGCTGT 720
TGGTCCAGAG ATGCCGAGTA CGGACTGTAC TCCATCTATC AGGGAGGATT GTTCGAGCTA 780
AAAAAAAATG ACAGGATTT TGTTCTGTG ACAAAATGAAC ATTTGATGGA CCTGGATCAA 840
GAAGCCAGCT TCTTGGAGC CTTTTAATT AACTAA 876

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 720 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

ATGGAGCCAG GGCTGCAACA AGCAGGCAGC TGTGGGGCTC CTTCCCCCTGA CCCAGCCATG 60
CAGGTGCAGC CGGGCTCGGT AGCCAGCCCC TGGAGAACCA CGAGGCCCTG GAGAACACA 120
AGTCGCAGCT ACTTCTACCT CAGCACCAACC GCACTGGTGT GCCTTGTGT GGCAGTGGCG 180
ATCATTCTGG TACTGGTAGT CCAGAAAAAG GACTCCACTC CAAATACAAC TGAGAAGGCC 240
CCCCTTAAAG GAGGAAATTG CTCAGAGGAT CTCTTCTGTA CCCTGAAAAG TACTCCATCC 300
AAGAAGTCAT GGGCCTACCT CCAAGTGTCA AAGCATCTCA ACAATACCAA ACTGTATGG 360
AACGAAGATG GCACCATCCA CGGACTCATA TACCAGGACG GGAACCTGAT AGTCAATTG 420
CCTGGCTTGT ACTTCATCGT TTGCCAACCTG CAGTCCCTCG TGCACTGCTC AAATCATTCT 480
GTGGACCTGA CATTGCAGCT CCTCATCAAT TCCAAGATCA AAAAGCAGAC GTGGTAACA 540
GTGTGTGAGT CTGGAGTTCA GAGTAAGAAC ATCTACCAGA ATCTCTCTCA GTTTTGCTG 600
CATTACTTAC AGGTCAACTC TACCATATCA GTCAGGGTGG ATAATTTCCA GTATGTGGAT 660
ACAAACACTT TCCCTCTTGA TAATGTGCTA TCCGTCTTCT TATATAGTAG CTCAGACTGA 720

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 930 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

ATGGACCAGC ACACACTTGA TGTGGAGGAT ACCGCGGATG CCAGACATCC AGCAGGTACT	60
TCGTGCCCT CGGATGCGGC GCTCCTCAGA GATAACGGGC TCCTCGCGGA CGCTGCGCTC	120
CTCTCAGATA CTGTGCGCC CACAAATGCC GCGCTCCCCA CGGATGCTGC CTACCCCTGCG	180
GTTAATGTTG GGGATCGCGA GGCGCGTGG CCGCCTGCAC TGAACTTCTG TTCCC GCCAC	240
CCAAAGCTCT ATGGCCTAGT CGCTTTGGTT TTGCTGCTTC TGATGCCGC CTGTGTT CCT	300
ATCTTCACCC GCACCGAGCC TCGGCCAGCG CTCACAATCA CCACCTCGCC CAACCTGGGT	360
ACCCGAGAGA ATAATGCAGA CCAGGT CACC CCTGTTCCC ACATTGGCTG CCCAACACT	420
ACACAAACAGG GCTCTCCTGT GTTCGCAAG CTACTGGCTA AAAACCAAGC ATCGTTGTGC	480
AATACAACCTC TGAAC TGCA CAGCCAAGAT GGAGCTGGGA GCTCATACCT ATCTCAAGGT	540
CTGAGGTAGC AAGAAGACAA AAAGGAGTTG GTGGTAGACA GTCCCGGGCT CTACTACGTA	600
TTTTTGGAAC TGAAGCTCAG TCCAACATTC ACAAACACAG GCCACAAGGT GCAGGGCTGG	660
GTCTCTCTTG TTTTGCAAGC AAAGCCTCAG GTAGATGACT TTGACAAC TT GGCCCTGACA	720
GTGGAAC TGT TCCCTTGCTC CATGGAGAAC AAGTTAGTGG ACCGTTCTG GAGTCAACTG	780
TTGCTCCTGA AGGCTGGCCA CCGCCTCAGT GTGGGTCTGA GGGCTTATCT GCATGGAGCC	840
CAGGATGCAT ACAGAGACTG GGAGCTGTCT TATCCAACA CCACCAGCTT TGGACTCTT	900
CTTGTGAAAC CCGACAAACCC ATGGGAATGA	930

PATENT
231/003

APPLICATION

FOR

UNITED STATES LETTERS PATENT

**NOVEL EXPRESSION VECTORS CONTAINING ACCESSORY
MOLECULE LIGAND GENES AND THEIR USE FOR
IMMUNOMODULATION AND TREATMENT OF
MALIGNANCIES AND AUTOIMMUNE DISEASE**

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I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

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231/003
Patent

Jeanette M. Olivera

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Jeanette M. Olivera
Signature

DESCRIPTION

NOVEL EXPRESSION VECTORS CONTAINING ACCESSORY MOLECULE
LIGAND GENES AND THEIR USE FOR IMMUNOMODULATION AND
TREATMENT OF MALIGNANCIES AND AUTOIMMUNE DISEASE

RELATED APPLICATION

This application claims priority to Kipps et al., NOVEL EXPRESSION VECTORS CONTAINING ACCESSORY MOLECULE 5 LIGAND GENES AND THEIR USE FOR IMMUNOMODULATION AND TREATMENT OF MALIGNANCIES, United States Provisional Application No. 60/132145, filed December 9, 1996, which is incorporated herein by reference including drawings.

10

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel expression vectors containing genes which encode an accessory molecule ligand and the use of those vectors for 15 immunomodulation, improved vaccination protocols and the treatment of malignancies and autoimmune diseases. More particularly, this invention provides expression vectors and methods for treating various neoplastic or malignant cells, and expression vectors and methods for treating 20 autoimmune Disease. This invention also contemplates the production and expression of accessory molecule ligands with greater stability and enhanced function.

25

BACKGROUND OF THE INVENTION

Leukemias, lymphomas, carcinomas and other malignancies are well known and described in, e.g., Harrison's Principles of Internal Medicine, Wilson et al., eds., McGraw-Hill, New York, pp. 1599-1612. These

malignancies appear to have somehow escaped the immune system surveillance mechanisms that eliminate rapidly and continuously proliferating cells. The exact mechanism by which these malignancies escape the immune system surveillance is not known.

Some of these malignant immune system cells are malignant antigen presenting cells which do not function properly within the immune cascade. For example, neoplastic B cells cannot induce even weak allogeneic or autologous mixed lymphocyte reactions in vitro. Further evidence that malignancies survive due to the failure of the immune surveillance mechanism includes the increased frequency of such malignancies in immunocompromised individuals, such as allograft recipients and those receiving long-term immunosuppressant therapy. Further, the frequency of these malignancies is increased in patients having Acquired Immune Deficiency Syndrome (AIDS) and patients with primary immune deficiency syndromes, such as X-linked lymphoproliferative syndrome or Wiscott-Aldrich Syndrome (Thomas et al., Adv. Cancer Res. 57:329, 1991).

The immune system normally functions to eliminate malignant cells by recognizing the malignant cells as foreign cells and clearing those cells from the body. An immune reaction depends on both the immune system's antibody response and on the cellular immune response within a patient. More specifically, the cellular immune response which acts to recognize the malignant cells as foreign requires a number of different cells of the immune system and the interaction between those cells. An immune reaction begins with a T lymphocyte (T cell) which has on its cell surface the T cell receptor. The T cell also has the ability to express on its surface various accessory molecules which interact with accessory molecules on the B lymphocyte (B cell). When

the T cell receptor of the T cell specifically binds to a foreign antigen, such as a malignant cell, it becomes activated and expresses the accessory molecule ligand, CD40 ligand on its cell surface. The accessory cell 5 molecule ligand is only present on the activated T cells for a short period of time and is rapidly removed from the cell surface. After the accessory cells molecule ligand is removed from the surface of the activated T cell, its ability to bind to B cells via the accessory 10 molecule ligand is destroyed.

When present on the surface of an activated T cell, the accessory cell ligand can specifically bind to the accessory cell molecule present on the B cell. This specific T-B cell interaction causes the B and T cell to 15 express costimulatory surface accessory molecule and cytokines which result in an immune activation which lead to cytolytic T cells which specifically kill and remove the malignant cell from the body.

The interaction with an activated T cell is not 20 solely limited to B cells but rather can be carried out by any cell which is able to present antigen to the T cell (an antigen presenting cell). These cells include B lymphocyte, macrophages, dendritic cells, monocytes, Langerhans cells, interdigitating cells, follicular 25 dendritic cells or Kupffer cells. These cells all are known to have various accessory molecules on the cell surface which allow them to interact with other cells of the immune system. For example, these antigen presenting cells all have the accessory molecule CD40 on 30 their cell surface. The presence of these accessory molecules allows these antigen presenting cells to specifically bind to complimentary accessory molecule ligand and thus directly interact with other immune cells.

A large number of accessory molecule ligands are members of the tumor necrosis factor superfamily. (Fanslow et al., Sem. Immun., 6:267-268 (1994)). The genes for a number of these accessory molecule ligands 5 have been cloned and identified. These accessory molecule ligand genes encode accessory molecules which all have the configuration of Type II membrane proteins and exhibit varying degrees of homology with other accessory molecule ligand genes. For example, the 10 accessory molecule ligand genes encoding both murine CD40 ligand and human CD40 ligand have been isolated. See, Armitage et al., Nature, 357:80-82 (1992) and Hollenbaugh et al., EMBO J., 11:4313-4321 (1992). CD40 and its ligand, CD40 ligand are critical 15 components of a normal immune response. CD40 mediated signals induce immune lymphocytes to proliferate and differentiate and become potent antigen presenting cells. Malignant or neoplastic B cells are poor antigen presenter cells and are unable to stimulate a vigorous 20 allogeneic mixed lymphocyte reaction. Successful cross linking of CD40 molecules on immune cells results in a strong allogeneic mixed lymphocyte reaction suggesting a strong immune reaction. Various soluble CD40 ligands or antibodies specific for CD40 have been used to 25 potentially cross link CD40. These soluble CD40 ligands and CD40-specific antibodies are not optimal for cross linking the CD40 molecules on antigen presenting cells and do not work as effectively as CD40 ligand expressed on a cell membrane to produce strong stimulation of 30 antigen presenting cells. These methods are also difficult to implement because large amounts of CD40 ligand constructs or antibodies must be isolated which is difficult and time-consuming work. Other strategies to utilize CD40 ligand in solution or as a membrane 35 bound molecule including transformation of fibroblasts

with CD40 ligand to produce cultured cells which are then used to present antigen are not amenable to in vivo human clinical protocols.

CD95 (Fas) interaction with its ligand (Fas-ligand, 5 or FasL) functions to limit the duration of the immune response and/or life-span of activated lymphocytes. Apoptosis induced by Fas-FasL binding serves to clear activated self-reactive lymphocytes. Problems caused by altering this pathway have been demonstrated in animals 10 with defects in Fas<->Fas-ligand interactions. Mice having mutations, which inactivate CD95 or FasL, develop numerous disorders including autoimmune pathology resembling that seen in patients with rheumatoid arthritis (RA) or systemic lupus. Zhang, et al., in J. Clin. Invest. 100:1951-1957 (1997) show that injection of FasL-expressing virus, into the joints of mice with collagen-induced-arthritis, results in apoptosis of synovial cells and relief of arthritis symptoms. Expression of Fas ligand allows clearance of activated 20 cells which play a role in the pathogenesis of autoimmune disease. Therefore, a gene therapy strategy for introducing FasL into the joints of rheumatoid arthritis patients could function to improve disease pathology by leading to destruction of the infiltrating 25 mononuclear cells.

Administration of soluble accessory molecules and accessory molecule ligands has been shown to trigger or to be associated with adverse physiological effects. For example, treatment of mice, having wild-type CD40- 30 receptor expression, with soluble CD40L-CD8 fusion protein resulted in a pulmonary inflammatory response. This was not observed in mice in which the gene for the CD40 receptor had been knocked out. These experiments, described in Wiley, J.A. et al., Journal of Immunology 35 158:2932-2938 (1997), support in vitro data which

suggest that CD40 ligation can result in inflammatory responses.

Direct administration of purified recombinant soluble Tumor Necrosis Factor (either α or β) results in 5 shock and tissue injury, as described in Tracey, K. J., and A. Cerami, Annu. Rev. Med. 45:491-503 (1994). Within minutes after acute intravenous or intra-arterial 10 administration of TNF, a syndrome of shock, tissue injury, capillary leakage syndrome, hypoxia, pulmonary edema, and multiple organ failure associated with a high 15 mortality ensues. Chronic low dose of TNF causes anorexia, weight loss, dehydration and depletion of whole-body protein and lipid.

Soluble Fas ligand and receptor have also been 15 shown to be associated with tissue damage and other adverse effects. CD95, the Fas receptor, is a mediator of apoptosis. Fas ligand induces apoptosis by binding to Fas receptor. As shown in Galle, P.R., et al., J. Exp. Med. 182:1223-1230 (1995) administering an 20 agonistic anti-Fas antibody resulted in liver damage to mice. Mice injected intraperitoneally with the agonistic antibody died within several hours, and analyses revealed that severe liver damage by apoptosis was the most likely cause of death.

The role of soluble Fas ligand (FasL), in the 25 pathogenesis of systemic tissue injury in aggressive lymphoma is described in Sato, K. et al., British Journal of Haematology, 94:379-382 (1996). The findings presented in this report indicate that soluble FasL is 30 directly associated with the pathogenesis of liver injury and pancytopenia.

CD27, the receptor for the accessory molecule ligand, CD70, was shown, in a report written by van Oers, et al., in Blood 82:3430-3436 (1993), to be 35 associated with B cell malignancies.

The above findings all contraindicate the administration of soluble accessory molecule ligands, highlighting the need for therapies that increase the levels of these molecules without resulting in an 5 elevation of their soluble forms.

Despite the wealth of information regarding accessory molecule ligand genes and their expression on the surface of various immune cells, the exact mechanism by which the accessory molecule ligand genes are 10 regulated on antigen presenting cells is not yet known. Without specific knowledge of the regulation of expression of accessory molecule ligand genes on these antigen presenting cells, altering the immune response by varying expression of an accessory molecule ligand 15 gene has to date not been possible. Without any specific knowledge as to how to regulate the expression of an accessory molecule ligand gene on an antigen presenting cell, it is not possible to alter the immune response towards malignant cells. Thus, there was a 20 need for a method of increasing the expression of an accessory molecule ligand gene on normal and malignant cells including antigen presenting cells.

Further, without the ability to regulate the expression of accessory molecule ligands, it is not 25 possible to alter the immune clearance of these cells.

SUMMARY OF THE INVENTION

The present invention fills these needs by 30 providing novel expression vectors containing accessory molecule ligand genes and methods for introducing those genes into normal and malignant antigen presenting cells thereby allowing the alteration of an immune response, the treatment of autoimmune diseases and the treatment 35 of various neoplasias. This invention provides vectors,

including gene therapy vectors which contain accessory molecule ligand genes. These vectors also contain the additional genetic elements, such as promoters, enhancers, polyadenylation signals (3' ends), which 5 allow that vector to be successfully placed within the cell and to direct the expression of the accessory molecule ligand gene in a cell. Such gene therapy vectors are capable of transforming animal cells directly and thereby introducing the accessory molecule 10 ligand gene into the cells of that animal in a form which can be utilized to produce accessory molecule ligands within that cell.

In other aspects of the present invention, the function of an accessory molecule ligand is modified by 15 altering the half life of the molecule on the cell surface or by changing the level of expression of that molecule on the cell surface. In preferred embodiments, the present invention provides accessory molecule ligands which are modified to improve the stability of 20 such accessory molecule ligands on the cell surface. Such increased stability may be accomplished using any of the disclosed methods of molecules described in this application, including chimeric molecules and molecules into which mutations have been introduced at least one 25 location. The present invention also contemplates increasing the expression of such a molecule.

The present invention also provides gene therapy vectors containing the accessory molecule ligand genes which are chimeric in that portions of the gene are 30 derived from two separate accessory molecule ligands which may or may not be from different species. The accessory molecule ligand genes of the present invention include genes which encode molecules of the tumor necrosis factor (TNF) family. The molecules which make 35 up the TNF family include TNF_α, TNF_β, CD40 ligand, Fas

ligand, CD70, CD30 ligand, 41BB ligand (4-1BBL), nerve growth factor and TNF-related apoptosis inducing ligand (TRAIL). In some embodiments of the present invention, the chimeric accessory molecule ligand genes of the 5 present invention contain at least a portion of a murine accessory molecule ligand gene together with portions of accessory molecule ligand genes derived from either mouse, humans or other species. Some preferred embodiments of the present invention utilize murine CD40 10 ligand genes and chimeric CD40 ligand genes containing at least a segment of the murine CD40 ligand gene together with at least a segment of the human CD40 ligand gene. The present invention contemplates chimeric accessory molecule ligand genes wherein 15 segments from the accessory molecule ligand gene of one species have been interchanged with segments from a second accessory molecule ligand gene which may optionally be from a different species. For example, in one preferred embodiment, the murine CD40 ligand gene 20 transmembrane and cytoplasmic domains have been attached to the extracellular domains of human CD40 ligand gene.

The present invention contemplates gene therapy vectors which are capable of directly infecting the human, mammal, insect, or other cell. The use of such 25 gene therapy vectors greatly simplifies inserting an accessory molecule ligand gene into those cells. The contemplated gene therapy vectors may be used in vivo or in vitro to infect the desired cell and are particularly useful for infecting malignant cells to effect sustained 30 high-level expression of a physiologic ligand.

The present invention also contemplates animal, mammal, and human cells containing a gene therapy vector which includes an accessory molecule ligand gene and sufficient genetic information to express that accessory 35 molecule ligand within that cell. In preferred

embodiments, the present invention also contemplates human neoplastic antigen presenting cells which contain the gene therapy vectors of the present invention or contain an accessory molecule ligand gene together with 5 a promoter and 3' end region.

The present invention also contemplates human cells and human neoplastic cells containing a gene therapy vector which includes a chimeric accessory molecule ligand gene. The present invention also contemplates 10 bacterial cells or animal cells containing accessory molecule ligand genes, chimeric accessory molecule ligand genes, murine accessory molecule ligand genes, human accessory molecule ligand genes, the gene therapy vectors of the present invention, the vectors of the 15 present invention, and a chimeric accessory molecule ligand gene together with a heterologous promoter, enhancer or polyadenylation sequence.

The present invention also contemplates methods of altering immune response within a human patient or the 20 immunoreactivity of human cells in vivo by introducing a gene which encodes an accessory molecule ligand gene into the human cells so that that accessory molecule ligand is expressed on the surface of those human cells. This method includes the introduction of the accessory 25 molecule ligand gene as part of a gene therapy vector or in association with a heterologous or native promoter, enhancer or polyadenylation signal. Some preferred embodiments of the present invention utilize 30 introduction of Fas ligand genes and chimeric Fas ligand genes, constructed as contemplated above for CD40, into human cells to alter their immunoreactivity. The present invention also includes methods in which such accessory molecule ligand genes are inserted into cells which have the accessory molecule to which the accessory

molecule ligand binds on the surface of the cell into which the accessory molecule ligand gene.

The present methods of altering immunoreactivity are applicable to all types of human, animal, and murine 5 cells including human neoplastic cells such as human lymphomas, leukemias and other malignancies. In preferred embodiments, this method is used to introduce the gene encoding the accessory molecule ligand into potential antigen presenting cells of a human patient or 10 cell which can stimulate bystandant antigen presenting cells. Such antigen presenting cells include monocytes, macrophages, B cells, Langerhans cells, interdigitating cells, follicular dendritic cells, Kupffer cells, and the like. The various antigen presenting cells may be 15 present as part of a known malignancy in a human patient such as leukemias, lymphomas, acute monocytic leukemia (AML), chronic lymphocytic leukemia (CLL), acute myelomonocytic leukemia (AMML), chronic myelogenous or chronic myelomonocytic leukemia (CMML) and thus would 20 include all tumors of any cell capable of presenting antigen to the human or animal immune system or are capable of stimulating bystandant antigen presenting cells. The present invention also contemplates modulating the immune system by introducing genes 25 encoding an accessory molecule ligand gene of the present invention into any number of different cells found in a patient, including muscle cells, skin cells, stromal cells, connective tissue cells, fibroblasts and the like.

30 The present invention also contemplates methods of treating neoplasias in either a human patient or an animal patient. In one preferred embodiment, the method comprises isolating the neoplastic cells from the human or animal patient and inserting into those isolated 35 cells the gene which encodes the chimeric accessory

molecule ligand or the accessory molecule ligand so that that molecule is expressed on the cell surface of those neoplastic cells or other somatic cells. The neoplastic cells are then infused back into the human or animal 5 patient and may then participate in an enhanced immune response.

The present invention also contemplates the co-infection or co-introduction of the accessory molecule ligand gene together with a gene which encodes a tumor 10 or carcinoma specific antigen. This combination of molecules are then expressed on the surface of the neoplastic cells and when those cells are introduced into the patient lead to the rapid immune response resulting in the destruction of those cells.

15 The present methods also include directly introducing the gene therapy vector or other vector carrying the accessory molecule ligand gene directly into the tumor or tumor bed of a patient. Upon entering the tumor bed of the patient, the gene therapy vector or 20 other vector enter the cells present in the tumor or tumor bed and then express the accessory molecule ligand gene on the surface of those cells. These cells then are able to participate fully in the human immune or animal immune response.

25 The present invention also contemplates methods of augmenting an immune response to a vaccine. The present method of vaccinating an animal against a predetermined organism or antigen by administering to that animal a vaccine which has a genetic vector containing an 30 accessory molecule ligand gene. Other embodiments of the present invention include vaccinating an animal by administering two separate genetic vectors, one containing the antigens from the organism to which immunity is desired by isolating the cells of the target 35 animal and contacting with those cells a vector encoding

at least one antigen from a predetermined organism so that the antigen is expressed by the cells and also contacting those cells with a different vector which expresses the accessory molecule ligand gene on the

5 surface of the animal's antigen presenting cells.

Together these two separate vectors produce a vaccination which is much stronger and of longer duration than is vaccination with antigen alone.

The present methods of vaccination are applicable
10 to vaccinations designed to produce immunity against a virus, a cell, a bacteria, any protein or a fungus. The present methods are also applicable to immunization against various carcinomas and neoplasias. In these
15 embodiments, the tumor antigen against which immunity is desired is introduced into the animal together with the genetic vector containing the accessory molecule ligand gene.

The present invention also contemplates methods of treating arthritis utilizing a gene therapy vector
20 encoding an accessory molecule ligand. Of particular interest for use with arthritis is the Fas ligand molecule in which the expression of Fas ligand activity has been increased in the joint and/or the stability of the Fas ligand activity on cells within the joint
25 enhanced. In other embodiments, the present invention contemplated methods of treating arthritis utilizing chimeric accessory molecule ligands and chimeric accessory molecule ligand genes. The present invention also contemplates both ex vivo therapy and in vivo
30 therapy of arthritis utilizing the expression vectors of the present invention together with the Fas ligand and modified versions of that molecule including chimeric molecules.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Figure 1 is a diagram showing a number of accessory molecule ligand genes and Domains I-IV of those genes as deduced from sequence data.

Figure 2. Figure 2 is a diagram showing example chimeric accessory molecule ligand genes. The domains derived from the murine accessory module are shown shaded.

Figure 3. Figure 3 shows the amount of either mouse or human CD40 ligand found on the surface of Hela or CLL cells infected with gene therapy vectors containing the genes encoding these molecules. Figure 3A shows uninfected Hela cells (shaded) and Hela cells infected with a gene therapy vector encoding murine CD40 ligand. Figure 3B shows uninfected Hela cells (shaded) and Hela cells infected with a gene therapy vector encoding human CD40 ligand. Figure 3C shows uninfected CLL cells (shaded) and CLL cells infected with a gene therapy vector encoding murine CD40 ligand. Figure 3D shows uninfected CLL cells (shaded) and CLL cells infected with a gene therapy vector encoding human CD40 ligand.

Figure 4. Figure 4 shows histograms of the increased expression of CD54 (Figure 4B) and CD80 (Figure 4D) on CLL cells into which a gene therapy vector containing the accessory molecule ligand gene (murine CD40 ligand gene) has been introduced. The shaded graph indicates control stain in FACS analysis and the open graph indicates staining with monoclonal antibodies immunospecific for either CD54 (Figures 4A and 4B) or CD80 (Figures 4C and 4D).

Figure 5. Figure 5 shows the cell proliferation as measured by ^{3}H -TdR incorporation of allogeneic T cells in response to various stimulation regimes. The CLL cells

containing a gene therapy vector expressing an accessory molecule ligand gene (the murine CD40 ligand gene) were introduced, stimulating allogeneic T cells to proliferate.

5 Figure 6. Figure 6 shows the production of gamma interferon (IFN γ) by allogeneic T cells stimulated with CLL cells containing an accessory molecule ligand gene.

10 Figure 7. Figure 7 shows the treatment of a neoplasia in an animal using a gene therapy vector containing an accessory molecule ligand gene of the present invention. The open squares show mice immunized with neoplastic cell not expressing an accessory molecule ligand of the present invention. Mice immunized with neoplastic cells expressing an accessory molecule ligand of the present invention are shown as the horizontal line at the top of the Figure and show no morbidity.

15 Figure 8. Figure 8 shows the production levels and stabilities of CD40 ligand and CD40 ligand transcript in CLL (upper graph) and normal blood mononuclear cells (lower graph).

20 Figure 9. Figure 9 shows the time course of transgene expression in CLL B cells infected with the accessory molecule ligand (CD40 ligand). The MFIR (mean fluorescence intensity ratio), comparing the fluorescence intensity of CD19 $^{+}$ CLL cells stained with PE-labeled CD40 ligand versus the same stained with a PE-labeled isotype control mAb at each time point, are represented by the closed circles connected by solid lines according to the scale provided on the left-hand ordinate.

25 Figure 10. Figure 10 shows changes in surface antigen phenotype of CLL B cells infected with a gene therapy vector containing an accessory molecule ligand, CD40 ligand. Shaded histograms represent staining of

uninfected CLL cells (thin lines) stained with nonspecific control antibody, open histograms drawn with thin lines represent uninfected CLL cells stained with FITC-conjugated specific mAb, and open histograms drawn with thick lines (labeled CD154-CLL) represent CLL cells infected with the accessory molecule ligand gene therapy vector and stained with FITC-conjugated specific mAb.

Figure 11. Figure 11 shows levels of CD27 produced in CLL cells infected with a gene therapy vector containing an accessory molecule ligand. Figure 11A shows that CD40L-infected CLL (CD154-CLL) cells express reduced levels of surface CD27. Open histograms represent staining of non-infected CLL cells (thin lines) or infected CLL (thick lines) with FITC-conjugated α CD27 mAb, respectively. Figure 11B shows production of soluble form of CD27 by CLL B cells.

Figure 12. Figure 12 shows allogeneic T cell responses induced by CLL cells infected with a gene therapy vector containing an accessory molecule ligand (CD40 ligand, also called CD154). Figure 12A indicates the concentration of IFN γ in the supernatants after stimulation of allogeneic T cells with CLL cells containing the accessory molecule ligand. Figure 12B shows cell proliferation, as assessed by incorporation of 3 H-thymidine. Figures 12C and 12D show secondary allogeneic T cell responses induced by CLL containing the accessory molecule ligand.

Figure 13. Figure 13 depicts autologous T cell responses induced by CLL B cells containing the accessory molecule ligand, CD40 ligand or CD154, and controls. Figure 13A shows incorporation of 3 H-thymidine by autologous T cells co-cultured with the CLL cells. Figure 13B shows the levels of human IFN γ produced by autologous T cells co-cultured with the CLL cells. In Figure 13C, the CTL activities of autologous T cells

induced by CLL B cells containing the accessory molecule ligand are graphed.

Figure 14. Figure 14 shows specificity of CTL for autologous CLL B cells. IFN γ concentration was assessed 5 in the supernatants after 48 h of culture (Figure 14A), and cytolytic activity was assessed at 3 h of culture (Figure 14B). In Figure 14C, mAb were added to the autologous leukemia target cells prior to the CTL assay.

Figure 15. Figure 15 shows that intercellular 10 stimulation plays a role in production of the phenotypic changes observed in CLL cells expressing the accessory molecule ligand. In Figure 15A, the effect of culture density on the induced expression of CD54 and CD80 following infection with a gene therapy vector 15 containing the accessory molecule ligand (CD40 ligand, CD154) is shown. Shaded histograms represent staining of leukemia B cells with a FITC-conjugated isotype control mAb. Open histograms represent CD154-CLL B cells, cultured at high or low density (indicated by 20 arrows), and stained with a FITC-conjugated mAb specific for CD54 or CD80. Figure 15B shows inhibition of CD154-CLL cell activation by anti-CD154 mAb. Figures 15C and 15D depict expression of immune accessory molecules on bystander non-infected CLL B cells induced by CLL cells 25 expressing the accessory molecule ligand. Shaded histograms represent staining with PE-conjugated isotype control mAb.

Figure 16. Figure 16 shows that the vector encoding 30 an accessory molecule ligand enhances immunization against β -gal in mice. Figure 16A shows that mice that received intramuscular injections of the pCD40L vector produced significantly more antibodies to β -gal than did mice injected with either the non-modified pcDNA3 vector or pCD40L. Figure 16B, ELISA analyses of serial 35 dilutions of sera collected at d28, shows that mice co-

injected with placZ and pCD40L had an eight-fold higher mean titer of anti- β -gal antibodies at d28 than mice treated with placZ + pcDNA3.

Figure 17. Figure 17 shows analysis of the IgG₁ and IgG_{2a} immune responses to intramuscular plasmid DNA immunizations with and without a vector, pCD40L, encoding an accessory molecule ligand. IgG_{2a} anti- β -gal antibodies predominated over IgG₁ subclass antibodies in the sera of mice injected with either placZ and pcDNA3 or placZ and pCD40L. In contrast, BALB/c mice injected with β -gal protein developed predominantly IgG₁ anti- β -gal antibodies, and no detectable IgG_{2a} anti- β -gal antibodies.

Figure 18. Figure 18 shows the comparison between injection of mice with a vector, pCD40L, encoding an accessory molecule ligand, at the same and different sites as placZ. Adjuvant effect of pCD40L requires co-injection with placZ at the same site.

Figure 19. Figure 19 shows that co-injection into dermis of a vector encoding an accessory molecule ligand, pCD40L, with placZ enhances the IgG anti- β -gal response in BALB/c mice.

Figure 20. Figure 20 shows that a vector encoding an accessory molecule ligand, pCD40L, enhances the ability of placZ to induce CTL specific for syngeneic β -gal-expressing target cells. Splenocyte effector cells, taken from mice which had received injections of placZ and pCD40L, specifically lysed significantly more cells than did splenocytes from mice that received control injections.

Figure 21. Figure 21 shows downmodulation of human CD40L, but not murine CD40L, in lung tumor cell lines that express CD40.

Figure 22. Figure 22A shows that CD40 binding induces enhanced expression of the tumor cell surface

markers CD95 (Fas), CD54 (ICAM-1), and MHC-I, in lung tumor cell lines. Figure 22B shows downmodulation of human CD40L by CD40-positive tumor cells.

5 Figure 23. Figure 23 shows the inhibition of Fas ligand expression by lymphocytes in the presence of RA synovial fluid.

Figure 24. Figure 24 shows an outline for a clinical trial of an accessory molecule ligand (CD40L) gene therapy treatment for B cell CLL.

10 Figure 25. Figure 25 shows a sequence line-up of human Fas ligand with human Fas ligand in which Domain III is replaced by Domain III of murine Fas ligand. The top protein sequence is native human Fas ligand. Domain III is underlined with the dotted line. The double underline indicates a putative MMP cleavage site. The bottom protein sequence is that of chimeric human-mouse Fas ligand. Domain III of the mouse Fas ligand (underlined with dotted line) is substituted for Domain III of human Fas ligand. The numbers correspond to the 15 amino acid sequence number using 1 for the start of the polypeptide sequence. The number of the first nucleotide base for the codon encoding the amino acid is 20 $1+3x(n-1)$, where n is the amino acid sequence number.

25 Figure 26. Figure 26 shows a sequence line-up of human Fas ligand with human Fas ligand in which Domain III has been replaced with Domain III of human CD70. The top protein sequence is native human Fas ligand, and the bottom sequence is that of chimeric Fas ligand, in which Domain III of human CD70 has been substituted for 30 Fas Domain III. Other markings are used similarly as in Figure 25.

Figure 27. Figure 27 shows a sequence line-up of human Fas ligand with human Fas ligand in which Domain I has been replaced with Domain III of human CD70. The 35 top protein is native human Fas ligand, and the bottom

protein sequence is that of chimeric Fas ligand, in which Domain III has been replaced with Domain I of human CD70. Other markings are used similarly as in Figure 25.

- 5 Figure 28. Figure 28 shows the amino acids around and at known matrix metalloproteinase (MMP) cleavage sites, as described in Smith, M.M. et al., Journal of Biol. Chem. 270:6440-6449 (95) and Nagase, H., and G.B. Fields, Biopolymers (Peptide Science) 40:399-416 (96).
10 The cleavage site is indicated with an arrow.

DETAILED DESCRIPTION OF THE INVENTION

All references cited herein are hereby incorporated
15 in their entirety by reference.

I. Definitions

An "accessory molecule ligand gene" is a gene which
20 encodes all or part of an accessory molecule ligand. The gene comprises at least the nucleotide sequence required to encode the functional portion of an accessory molecule ligand. The gene may optionally include such genetic elements as promoters, enhancers
25 and 3' ends. The accessory molecule ligand gene is derived from a ligand which is a member of the tumor necrosis factor (TNF) family, including CD40 ligand, Fas ligand, CD70, TNF_α, TNF_β, CD30 ligand, 4-1BB ligand (4-1BBL), nerve growth factor and TNF-related apoptosis
30 inducing ligand (TRAIL). As used herein, the term "accessory molecule ligand gene" includes chimeric accessory molecule ligand genes as defined below.

As used herein, the term "malignant cells or neoplastic cells," is defined to mean malignant or
35 cancerous cells which are found in a human patient or an

animal. Preferred types of malignant or neoplastic cells include any malignant antigen-presenting cell. In some preferred embodiments, these malignant antigen presenting cells have at least low levels of CD40 present on the cell surface.

As used herein, the term "neoplastic human cells" is defined to mean human cells which are neoplastic including but not limited to antigen presenting cells, any neoplastic cell which may function as an antigen presenting cell or function to facilitate antigen presentation, neoplastic monocytes, neoplastic macrophages, neoplastic B cells, neoplastic dendritic cells, neoplastic Langerhans cells, neoplastic interdigitating cells, neoplastic follicular dendritic cells, or neoplastic Kupffer cells and the like. The definition of neoplastic human cells includes those cells which are associated with neoplastic cells in the tumor bed of human patients. Typically, the neoplastic human cells are either leukemias, lymphomas, AML, ALL, AMML, CML, CMML, CLL other tumors of antigen presenting cells or breast, ovarian or lung neoplastic cells. It is also contemplated that the accessory molecule ligand genes or chimeric accessory molecule ligand genes of the present invention may be inserted into somatic cells. These somatic cells can be created by a genetic engineering process which has introduced into those cells genes which encode molecules which render those cells capable of presenting antigen to the immune system.

As used herein, the term "chimeric gene" is defined to mean a gene in which part of the gene is derived from a second different gene and combined with the first gene so that at least a portion of each gene is present in the resulting chimeric gene. A gene may be chimeric if any portion of the sequence which encodes the resulting

protein is derived from a second and different gene. Typical chimeric genes include genes in which specific functional domains from one gene have been transferred to a second gene and replace the analogous domains of 5 that second gene. For example, the resulting chimeric gene may have one domain derived from a murine gene and several domains derived from a human gene. These domains may range in size from 5 amino acids to several hundred amino acids. Other examples of chimeric 10 accessory molecule ligand genes include genes which contain nucleotides encoding amino acids not found in any naturally occurring accessory molecule ligand gene. Examples of chimeric genes and potential various combinations of domains are numerous and one of skill in 15 the art will understand that no limit is placed on the amount of one gene that must be present in a second gene to render it chimeric.

As used herein, the term "murine CD40 ligand gene" is defined to mean an accessory molecule ligand gene 20 which is derived from a murine CD40 ligand gene. Examples of such murine CD40 ligand genes include the gene isolated by Armitage et al., Nature, 357:80-82 (1992) and other genes derived from murine origin which hybridize to the gene described by Armitage et al. under 25 low stringency hybridization conditions.

As used herein, the term "vector or genetic vector" is defined to mean a nucleic acid which is capable of replicating itself within an organism such as a bacterium or animal cell. Typical genetic vectors 30 include the plasmids commonly used in recombinant DNA technology and various viruses capable of replicating within bacterial or animal cells. Preferred types of genetic vectors includes plasmids, phages, viruses, retroviruses, and the like.

As used herein, the term "gene therapy vector" is defined to mean a genetic vector which is capable of directly infecting cells within an animal, such as a human patient. A number of gene therapy vectors have 5 been described in the literature, and include, the gene therapy vector described in Cantwell et al., Blood, In Press (1996) entitled "Adenovirus Vector Infection of Chronic Lymphocytic Leukemia B Cells." Such vectors have been described for example by Woll, P. J. and I. R. 10 Hart, Ann. Oncol., 6 Suppl 1:73 (1995); Smith, K. T., A. J. Shepherd, J. E. Boyd, and G. M. Lees, Gene Ther., 3:190 (1996); Cooper, M. J., Semin. Oncol., 23:172 (1996); Shaughnessy, E., D. Lu, S. Chatterjee, and K. K. Wong, Semin. Oncol., 23:159 (1996); Glorioso, J. C., N. 15 A. DeLuca, and D. J. Fink, Annu. Rev. Microbiol., 49:675 (1995); Flotte, T. R. and B. J. Carter, Gene Ther., 2:357 (1995); Randrianarison-Jewtoukoff, V. and M. Perricaudet, Biologicals, 23:145 (1995); Kohn, D. B., Curr. Opin. Pediatr., 7:56 (1995); Vile, R. G. and S. J. 20 Russell, Br. Med. Bull., 51:12 (1995); Russell, S. J., Semin. Cancer Biol., 5:437 (1994); and Ali, M., N. R. Lemoine, and C. J. Ring, Gene Ther., 1:367 (1994). All references cited herein are hereby incorporated by reference.

25

II. Genetic Vectors and Constructs Containing an Accessory Molecule Ligand Gene

A. Accessory Molecule Ligand Genes

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In one embodiment of the present invention, preferred gene therapy vectors contain an accessory molecule ligand gene. This accessory molecule ligand gene may be derived from any source and may include 35 molecules which are man-made and do not appear in

nature. The present invention contemplates accessory molecule ligand genes which are derived from the genes encoding molecules within the tumor necrosis family (TNF) which includes the genes encoding: murine CD40 ligand, human CD40 ligand, Fas ligand, TNF_α, TNF_β, CD30 ligand, 4-1BB ligand, nerve growth factor, CD70, TNF-related apoptosis inducing ligand (TRAIL) and chimeric accessory molecule ligands. The nucleotide sequence of one accessory molecule ligand, the sequence of at least 10 one form of the murine CD40 ligand gene, has been determined and is listed as SEQ ID NO: 1. The present invention contemplates the use of any accessory molecule ligand gene which is homologous to the sequence present in SEQ ID NO: 1, and thus hybridizes to this sequence at 15 low stringency hybridization conditions. One of skill in the art will understand that accessory molecule ligand genes, including murine CD40 ligand gene, useful in the present invention may be isolated from various different murine strains.

20 The nucleotide sequence of a human CD40 ligand gene has been determined and is shown as SEQ ID NO: 2. The present invention contemplates the use of any accessory molecule ligand gene which is homologous to SEQ ID NO: 2, and thus hybridizes to this sequence at low 25 stringency conditions. One of ordinary skill in the art will understand that the accessory molecule ligand genes, including the human CD40 ligand genes, useful in the present invention, may vary depending on the individual from which the gene is isolated and such 30 variations may prove useful in producing unique accessory molecule ligand genes. The present invention contemplates the use of the domains, sub-domains, amino acid or nucleotide sequence of the human CD40 ligand and/or human CD40 ligand gene as part of a chimeric

accessory molecule ligand or chimeric accessory molecule ligand gene.

The nucleotide sequence of a bovine CD40 ligand gene has been determined and is shown as SEQ ID NO: 8.

- 5 The present invention contemplates the use of any accessory molecule ligand gene which is homologous to SEQ ID NO: 8, and thus hybridizes to the sequence at low stringency conditions. One of ordinary skill in the art will understand that the accessory molecule ligand genes, including the bovine CD40 ligand genes, may vary depending on the individual animal from which the gene is isolated and that such variations may prove useful in producing unique accessory molecule ligand genes.

The nucleotide sequence of human TNF_α and human TNF_β have been determined and are shown as SEQ ID NOS: 9 and 10, respectively. The present invention contemplates the use of any accessory molecule ligand gene which is homologous to either human TNF_α or human TNF_β (SEQ ID NOS: 9 and 10, respectively), and thus hybridizes to these sequences at low stringency conditions. The accessory molecule ligand genes useful in the present invention, including the human TNF_α and TNF_β genes, may vary depending on the particular individual from which the gene has been isolated and these variations may prove useful in producing unique accessory molecule genes.

The nucleotide sequence of porcine TNF_α and TNF_β have been determined and are shown as SEQ ID NO: 11.

- 30 The present invention contemplates the use of any accessory molecule ligand gene which is homologous to either SEQ ID NO: 11, and thus would hybridize to these sequences at low stringency conditions. One of ordinary skill in the art will understand that the accessory molecule ligand genes, including the porcine TNF_α and TNF_β genes, may vary depending on the particular animal

from which the gene is isolated and that such variation may prove useful in producing unique accessory molecule genes.

The nucleotide sequence of a murine TNF_α gene has
5 been determined and is shown as SEQ ID NO: 12. The present invention contemplates the use of any accessory molecule ligand gene which is homologous to SEQ ID NO: 12, and thus hybridizes to the sequence at low stringency conditions. One of ordinary skill in the art 10 will understand that the accessory molecule ligand genes, including the murine TNF_α gene may vary depending on the individual from which the gene is isolated and that these variations may prove useful in producing unique accessory molecule genes.

15 The nucleotide sequence of human Fas ligand and murine (C57BL/6) Fas ligand have been determined and are shown as SEQ ID NOS: 13 and 14, respectively. The nucleotide sequence of murine Balb/c Fas ligand is shown as SEQ ID NO: 31. The present invention contemplates 20 the use of any accessory molecule ligand gene which is homologous to any of SEQ ID NOS: 13, 14, and 31, and thus hybridizes to the sequences at low stringency conditions. One of ordinary skill in the art will understand that the accessory molecule ligand genes, 25 including the human Fas ligand or murine Fas ligand genes may vary depending on the particular individual or animal from which the gene is isolated and that such variations may prove useful in producing any accessory molecule genes.

30 The nucleotide sequence of a human CD70 gene has been determined and is shown as SEQ ID NO: 15. The murine CD70 gene sequence has also been determined, and is shown as SEQ ID NO: 36 and was described by Tesselaar et. al, J. Immunol. 159:4959-65(1997). The present 35 invention contemplates the use of any accessory molecule

ligand gene which is homologous to SEQ ID NO: 15 or 36, and thus hybridizes to this sequence at low stringency conditions. One of ordinary skill in the art will understand that the accessory molecule ligand genes, 5 including the human CD70 gene may vary depending on the individual from which the gene is isolated and that these variations may prove useful in producing unique accessory molecule ligand genes.

The nucleotide sequence of human CD30 ligand gene 10 has been determined and is shown as SEQ ID NO: 16. The present invention contemplates the use of any accessory molecule ligand gene which is homologous to SEQ ID NO: 16, and thus hybridizes to this sequence at low stringency conditions. One of ordinary skill in the art 15 will understand that the accessory molecule ligand genes, including the human CD30 ligand gene, may vary depending on the individual from which the gene is isolated and that such variations may prove useful in producing unique accessory molecule ligand genes.

20 The present invention also contemplates variations and variants of the nucleotide sequences of the accessory molecule ligand genes provided herein which are caused by alternative splicing of the messenger RNA. This alternative splicing of the messenger RNA inserts 25 additional nucleotide sequences which may encode one or more optional amino acid segments which in turn allows the accessory molecule ligand encoded to have additional properties or functions.

The nucleotide sequence of a human and mouse 4-1BBL 30 have been determined and are shown as SEQ ID NOS: 17 and 18, respectively. The present invention contemplates the use of any accessory molecule ligand gene which is homologous to either SEQ ID NOS: 17 or 18, and thus hybridizes to these sequences at low stringency 35 conditions. One of ordinary skill in the art will

understand that accessory molecule ligand genes, including the human 4-1BBL gene may vary depending on the individual from which it is isolated and that such variations may prove useful in producing unique
5 accessory molecule ligand genes.

The present invention also contemplates chimeric accessory molecules containing any domain, sub-domain portion, or amino acid sequence encoded by the following genes: bovine TNF- α (SEQ ID NO: 21), murine CD40 ligand
10 (SEQ ID NO: 22), human nerve growth factor- β (SEQ ID NO: 23), murine nerve growth factor (SEQ ID NO: 24), rat Fas ligand (SEQ ID NO: 25), human TNF-related apoptosis inducing ligand (TRAIL) (SEQ ID NO: 41, Genbank accession number U37518), murine TNF-related apoptosis
15 inducing ligand (TRAIL) (SEQ ID NO: 42, Genbank accession number U37522), murine CD30-Ligand (SEQ ID NO: 43), human 4-1BBL (SEQ ID NO: 17), and murine 4-1BBL (SEQ ID NOS: 44 and 18). The present invention also contemplates chimeric accessory molecules which utilize
20 genes encoding amino acid sequences homologous to these sequences.

The present invention contemplates chimeric accessory molecule ligand genes which are comprised of a nucleotide segment derived from one accessory molecule
25 ligand gene operatively linked to a nucleotide sequence derived from a different accessory molecule ligand gene or other gene.

For example, chimeric accessory molecule ligand genes are contemplated which are comprised of a segment
30 of the murine CD40 ligand gene which has been operatively linked to at least one other additional gene segment derived from a different accessory molecule ligand gene. The size of the particular segment derived from the different accessory molecule ligand gene may
35 vary from a nucleotide sequence encoding a few amino

acids, a sub-domain of the accessory molecule ligand, a domain of the accessory molecule ligand or more than a domain of an accessory molecule ligand. Other chimeric accessory molecules of the present invention are

5 comprised of an accessory molecule ligand gene into which nucleotides encoding an amino acid segment which is not found as part of a naturally occurring accessory molecule ligand have been inserted. This amino acid segment may be artificially created or derived from a

10 protein found in nature. The chimeric accessory molecule ligand gene encodes a chimeric amino acid sequence and thus a chimeric accessory molecule ligand encoded may possess unique properties in addition to the properties found on the individual segments derived from

15 the different accessory molecule ligand genes. The chimeric accessory molecule ligand gene may encode an accessory molecule ligand which has properties derived from the accessory molecule ligand used to construct the chimeric gene.

20 Each of the accessory molecule ligand genes which are a member of the tumor necrosis factor family have a similar secondary structure consisting of a number of domains. This domain structure includes a first domain which is encoded by the 5' region of the accessory

25 molecule ligand gene. The second domain (Domain II) is the domain which contains the amino acids which span the cell membrane and is thus called the transmembrane domain. The third domain (Domain III) is the proximal extracellular domain and these amino acids are the amino

30 acids which are found proximal to the cellular membrane. The fourth domain (Domain IV), is encoded by the 3' end of the accessory molecule ligand gene and has been called the distal extracellular domain. The distal extracellular domain (Domain IV) generally makes up the

35 soluble form of the tumor necrosis factor family

molecule. Based on the x-ray crystal structure of human TNF, the predicted secondary structure of the accessory molecule, CD40 ligand has been deduced together with the domain structure of these molecules by M. Peitsch and C.

5 Jongeneel, International Immunology, 5:233-238 (1993). The secondary structures of the other members of the tumor necrosis factor family were deduced using computer analysis together with comparison to the human TNF and CD40 ligand domain structure. In Table I, the domain

10 boundaries of a number of accessory molecule ligand genes is shown. A diagram of these domains for a number of these accessory cell molecule ligands is shown in Figure 1. The assignments of the domain boundaries are approximate and one of ordinary skill in the art will understand that these boundaries may vary and yet still provide useful identification of domains.

15

TABLE I
DOMAIN STRUCTURE OF TUMOR NECROSIS
FACTOR FAMILY MOLECULES*

		Domain I (Cytoplasmic)	Domain II (Transmembrane)	Domain III (Proximal Extracellular)	Domain IV (Distal Extracellular)
5	Human CD40 Ligand	1-42	43-135	136-330	331-786
	Murine CD40 Ligand	1-42	43-135	136-327	328-783
10	Bovine CD40 Ligand	1-42	43-135	136-330	331-786
	Human TNF- α	1-87	88-168	169-228	229-699
15	Murine TNF- α	1-87	88-168	169-237	238-705
	Porcine TNF- α	1-87	88-168	169-228	229-696
20	Human TNF- β	1-39	40-129	130-153	154-615
	Porcine TNF- β	1-39	40-126	127-150	151-612
25	Human Fas Ligand	1-237	238-315	316-390	391-843
	Murine Fas Ligand	1-237	238-309	310-384	385-837
30	Human CD70	1-61	62-117	118-132	133-579
	Murine CD70	1-73	74-123	124-138	139-585
35	Human CD30 Ligand	1-117	118-186	187-240	241-702
	Murine CD30 Ligand	1-135	136-201	202-255	256-717
	Human 4-1BBL	1-69	70-174	175-210	211-762
	Murine 4-1BBL	1-237	238-333	334-369	370-927
	Human TRAIL	1-39	40-117	118-375	376-843
	Murine TRAIL	1-51	52-111	112-387	388-873

* The Domains above are identified by the nucleotide boundaries of each domain using the first nucleotide of the initial methionine of the cDNA as nucleotide number 1.

One of ordinary skill in the art will understand that typical chimeric accessory molecule genes would include genes produced by exchanging domains or sub-domain segments between, for example, a mouse CD40 ligand gene and a human CD40 ligand gene. For example, chimeric accessory molecule gene may be constructed by operatively linking Domain I of the human CD40 ligand gene to Domains II-IV of the murine CD40 ligand gene.

One of ordinary skill in the art will understand the variety of chimeric accessory molecule ligand genes which may be produced using the accessory molecules identified in Table I. The present invention also contemplates chimeric accessory molecules which are not shown in Table I but which are shown to have a similar domain structure. Other chimeric genes are also contemplated in which smaller segments (sub-domain segments) are exchanged between, for example, a murine CD40 ligand gene and a human CD40 ligand gene or a second murine CD40 ligand gene. One of skill in the art will understand that genes encoding accessory molecules will have at least gene segments which correspond to various functional segments of an accessory molecule ligand such as the murine CD40 ligand encoded by the murine CD40 ligand gene (SEQ ID NO: 1). It will also be apparent to one of skill in the art that the nucleotide boundaries identified in Table I may vary considerably from those identified for the murine CD40 ligand gene (SEQ ID NO: 1) and still define domains which are useful in the present invention.

In one preferred embodiment, the chimeric accessory molecule ligand gene is comprised of the nucleotides encoding extracellular domains (Domains III and IV) of human CD40 ligand operatively linked to the nucleotides encoding transmembrane (Domain II) and the nucleotides encoding cytoplasmic domain (Domain I) of the murine

CD40 ligand gene. Examples of such preferred chimeric accessory molecules are shown in Figure 2. An exemplary nucleotide sequence for such a gene is SEQ ID NO: 7. In other chimeric accessory molecule ligand genes of the present invention, the nucleotides encoding the extracellular domains (Domains III and IV) of the murine CD40 ligand gene may be operatively linked to nucleotides encoding the transmembrane (Domain II) and cytoplasmic domain (Domain I) of the human CD40 ligand gene. An exemplary nucleotide sequence for such a gene is SEQ ID NO: 3. In other preferred chimeric accessory molecule ligand genes of the present invention, the nucleotides encoding the extracellular domains (Domains III and IV) and transmembrane domain (Domain II) of human CD40 ligand are coupled to the nucleotides encoding cytoplasmic domain (Domain I) of murine CD40 ligand gene. An exemplary nucleotide sequence for such a gene is SEQ ID NO: 6. Other chimeric accessory molecule genes contemplated by the present invention comprise the nucleotides encoding the extracellular domains (Domains III and IV) and transmembrane domain (Domain I) of the murine CD40 ligand gene operatively linked to the nucleotides encoding cytoplasmic domain of the human CD40 ligand gene. An exemplary nucleotide sequence for such a gene is SEQ ID NO: 5. Other chimeric accessory molecule ligand genes are contemplated by the present invention in which the human CD40 ligand gene extracellular domains (Domain III and IV) is operatively linked to the murine CD40 ligand gene transmembrane domain (Domain I) which is operatively linked to the human CD40 ligand gene cytoplasmic domain (Domain I). An exemplary nucleotide sequence for such a gene is SEQ ID NO: 4.

One of ordinary skill in the art will understand that many more combinations which utilize domains or

other selected segments of any of the accessory molecule ligand genes including the human CD40 ligand genes and the mouse CD40 ligand genes are possible. Such additional chimeric accessory molecule genes would

5 include the following genes: chimeric accessory molecule genes in which the nucleotides encoding Domain I are selected from a particular accessory molecule ligand gene and operatively linked, either directly or by an additional nucleotide sequence to the nucleotides

10 encoding Domain II from a particular accessory molecule ligand gene. These domains then would be operatively linked either directly or by an additional nucleotide sequence to the nucleotides encoding Domain III from a particular accessory molecule ligand gene. This

15 molecule would then be operatively linked either directly or by an additional nucleotide sequence to the nucleotides encoding Domain IV of a particular accessory molecule ligand gene. The chimeric accessory molecule ligand gene constructed in this manner may have

20 additional nucleotides on either end or between domains which are useful to provide different amino acids in these positions. One of ordinary skill in the art will understand that these particular combinations are merely illustrations and that numerous other combinations could

25 be contemplated in which gene segments comprising nucleotides encoding less than the entire domain of an accessory molecule are exchanged between different accessory molecules.

The present invention also contemplates chimeric

30 accessory molecule ligand genes which are comprised of gene segments of mouse or human CD40 ligand in combination with gene segments derived from Fas ligand, TNF_α, TNF_β, CD70, CD30L, 4-1BBL, nerve growth factor or TNF-related apoptosis inducing ligand (TRAIL).

35 Particularly useful chimeric accessory molecule ligand

genes comprise at least one gene segment which is derived from a murine CD40 ligand gene together with gene segments or a gene segments derived from a different accessory molecule ligand gene.

5 The present invention also contemplates chimeric accessory molecule ligand genes in which the accessory molecules produced have been modified to remove amino acids within the chimeric accessory molecule that are used by post-translational mechanisms to regulate the
10 level of expression of the accessory molecule or accessory molecule protein on a particular cell. The sites removed from the chimeric accessory molecules or chimeric molecule may include amino acids or sites which make up protease cleavage sites including
15 metallothionein proteases, serine proteases and other proteases that recognize an amino acid sequence either specifically or nonspecifically. In particular preferred embodiments, amino acids in Domain III which make up potential or actual recognition site(s) used by
20 post-translational regulatory mechanisms have been modified or removed.

 The present invention also contemplates chimeric accessory molecule ligand genes in which the domains, subdomain fragments or other amino acid residues have been taken from one accessory molecule ligand gene and moved into a second accessory molecule ligand gene from the same species. For example, in this particular embodiment, the human Domain I, and the human Domain II from the CD40 ligand molecule may be operatively linked
25 to the nucleotides encoding the human Domain III from, for example, the CD70 molecule which is in turn operatively linked to human Domain IV for the CD40 ligand molecule. This chimeric accessory molecule therefore contains human CD40L Domains I, II and IV and
30 human CD70 Domain III. An exemplary nucleotide sequence
35

for such a gene is SEQ ID NO: 19. One of ordinary skill in the art will understand that a number of such combinations using domains from the same species from different accessory molecule ligand genes may create a 5 number of chimeric accessory molecule genes which may all have specific activities and properties.

The present invention contemplates chimeric accessory molecule ligand genes in which the Domain III of a particular accessory molecule ligand gene has been 10 replaced with a Domain III from a different accessory molecule ligand gene. In one particularly preferred embodiment, the mouse Domain III has been used to replace the human Domain III in the CD40 ligand molecule. This chimeric accessory molecule therefore 15 contains the human CD40L Domain I, the human CD40L Domain II, mouse CD40L Domain III, and human CD40L Domain IV. An exemplary nucleotide sequence for such a gene is SEQ ID NO: 20.

The present invention also contemplates the use of 20 chimeric accessory molecules that contain man-made amino acid sequences inserted into or in place of a portion of a domain or other amino acid sequence of an accessory molecule gene. These man-made amino acid segments may be created by selecting any amino acid sequence that may 25 be used to give the accessory molecule a particular function or to remove another undesired function. These man-made amino acid segments are produced by inserting into the accessory molecule ligand gene or chimeric accessory molecule ligand gene the nucleotide sequences 30 required to encode those particular man-made amino acid segments in the desired positions. Further, the chimeric accessory molecule ligand genes may contain nucleotide segments which comprise sub-domain segments of other molecules or small segments in which amino 35 acids have been changed for a desired purpose. The use

of sub-domain nucleotide segments allows the introduction of short amino acid sequences derived from other molecules into chimeric accessory molecules of the present invention. The incorporation of such short sub-
5 domain segments or amino acid changes into the accessory molecule ligand allows the introduction of desired or the removal of undesired features of that molecule.

The identification of domain structures within accessory cell molecules is well known in the art and
10 generally requires the identification of cysteine residues within the accessory molecules and the subsequent mapping of disulfide bonds between various cysteine residues. The mapping of various sub-domain segments of an accessory molecule is well known in the
15 art and involves analysis of the amino acid sequence of the accessory molecules and generally involves a comparison of the crystal structure of tissue necrosis factor with the use of predictive algorithms thereby producing a predicted structure of a chimeric accessory
20 molecule or an accessory molecule. This predicted structure of these molecules can then be used to select various sub-domain portions of the molecule to be used to construct further chimeric accessory molecules.
Examples of such mapping studies include the studies by
25 M. Pitsch and C. V. Jongeneel, International Immunology, 5:233-238 (1993) and the analysis shown in Figure 1.

The present invention also contemplates accessory molecule ligand genes and chimeric accessory molecule ligand genes which are truncated and encode less than
30 the full length of the amino acid sequence found in the native accessory molecule ligand. These truncations may alter the properties of the accessory molecule ligand gene but some identified activity is maintained. Such truncations may be made by removing a gene segment or
35 gene segments from the accessory molecule gene and

typically would be performed by removing nucleotides encoding domains which are not directly involved in the binding of the accessory molecule ligand with its accessory molecule. These truncated accessory molecule 5 ligand genes or chimeric truncated accessory molecule ligand genes may contain further gene segments which encode amino acid segments or domains which replace the domains removed from that truncated accessory molecule gene. However, such replacement of the portions of the 10 accessory molecule removed by truncation is not necessary.

The chimeric accessory molecule genes of the present invention may be constructed using standard genetic engineering methods to operatively link a 15 particular nucleotide sequence from one accessory molecule ligand gene to a different nucleotide sequence derived from the same or different accessory molecule ligand gene. In addition, standard genetic engineering methods may be used to insert man-made nucleotide 20 sequences or sub-domain nucleotide sequences into the chimeric accessory molecule ligand gene. One of ordinary skill in the art will understand that various methods may be utilized to produce such chimeric accessory molecule genes. For example, a gene 25 conversion method known as "SOEN" may be used to produce a chimeric accessory molecule gene which contains nucleotide segments derived from different chimeric accessory molecules. The methods for using this gene conversion method are well known in the art and have 30 been described for example in Horton, R. M., Mol. Biotechnol., 3:93 (1995); Ali, S. A. and A. Steinkasserer, Biotechniques, 18:746 (1995); Vilardaga, J. P., E. Di Paolo, and A. Bollen, Biotechniques, 18:604 (1995); Majumder, K., F. A. Fattah, A. Selvapandiyar, 35 and R. K. Bhatnagar, PCR. Methods Appl., 4:212 (1995);

Boles, E. and T. Miosga, Curr. Genet. 28:197 (1995);
Vallejo, A. N., R. J. Pogulis, and L. R. Pease, PCR.
Methods Appl., 4:S123 (1994); Henkel, T. and P. A.
Baeuerle, Anal. Biochem., 214:351 (1993); Tessier, D. C.
5 and D. Y. Thomas, Biotechniques, 15:498 (1993);
Morrison, H. G. and R. C. Desrosiers, Biotechniques,
14:454 (1993); Cadwell, R. C. and G. F. Joyce, PCR.
Methods Appl., 2:28 (1992); and, Stappert, J., J.
Wirsching, and R. Kemler, Nucleic Acids Res., 20:624
10 (1992). Alternatively, one of ordinary skill in the art
will understand that site-directed mutagenesis may be
used to introduce changes into a particular nucleotide
sequence to directly produce or indirectly be used to
produce a chimeric accessory molecule gene of the
15 present invention. For example, the mutagen kit
provided by BioRad Laboratories may be used together
with the methods and protocols described within that kit
to produce the desired changes in the nucleotide
sequence. These methods were originally described by
20 Kunkel, Proc. Natl. Acad. Sci. USA, 82:488-492 (1985)
and Kunkel et al., Meth. Enzol. Mol., 154:367-382
(1987). By using the site directed mutagenesis protocols
described herein and known within the art, a skilled
investigator may induce individual nucleotide changes
25 which result in an altered amino acid sequence or which
preserve an amino acid sequence but introduce a desired
restriction enzyme recognition sequence into the gene.
This new restriction endonuclease recognition site may
then be used to cut the gene at that particular point
30 and use it to a gene or segment of another accessory
molecule ligand gene. In addition to these methods, one
of ordinary skill in the art will understand that an
entire chimeric accessory molecule ligand gene may be
synthesized using synthetic methods known in the art.
35 This methodology only requires that the skilled artesian

generating nucleotide sequence of a chimeric accessory molecule ligand gene and provide that sequence to a company which is capable of synthesizing such a gene.

5 B. Genetic Constructs

The present invention contemplates the use of accessory molecule ligand genes or chimeric accessory molecule ligand genes which are present in various types 10 of genetic vectors. A genetic vector refers to a DNA molecule capable of autonomous replication in a cell into which another DNA segment can be inserted to cause the additional DNA segments to replicate. Vectors capable of expressing genes contained in that vector are 15 referred to as "expression vectors." Thus, the genetic vectors and expression vectors of the present invention are recombinant DNA molecules which comprise at least two nucleotide sequences not normally found together in nature.

20 The genetic vectors useful in the present invention contain an accessory molecule ligand gene which encodes an accessory molecule ligand which is optionally operatively linked to a suitable transcriptional or translational regulatory nucleotide sequence, such as 25 one derived from a mammalian, microbial, viral, or insect gene. Such regulatory sequences include sequences having a regulatory role in gene expression, such as a transcriptional promoter or enhancer, an operator sequence to control transcription, a sequence 30 encoding a ribosomal binding site within the messenger RNA and appropriate sequences which control transcription, translation initiation or transcription termination.

Particularly useful regulatory sequences include 35 the promoter regions from various mammalian, viral,

microbial, and insect genes. The promoter region directs an initiation of transcription of the gene and causes transcription of DNA through and including the accessory molecule ligand gene. Useful promoter regions 5 include the promoter found in the Rous Sarcoma Virus (RSV) - long terminal repeat (LTR), human cytomegalovirus (HCMV) enhancer/promoter region lac promoters, and promoters isolated from adenovirus, and any other promoter known by one of ordinary skill in the 10 art would understand to be useful for gene expression in eukaryotes, prokaryotes, viruses, or microbial cells. Other promoters that are particularly useful for expressing genes and proteins within eukaryotic cells include mammalian cell promoter sequences and enhancer 15 sequences such as those derived from polyoma virus, adenovirus, simian virus 40 (SV40), and the human cytomegalovirus. Particularly useful are the viral early and late promoters which are typically found adjacent to the viral origin of replication in viruses 20 such as the SV40. Examples of various promoters which have been used in expression vectors have been described by Okiama and Berg (Mol. Cell. Biol. 3:280, 1983), the pMLSVN SV40 described by Kossman et al., Nature 312:768 (1984). One of ordinary skill in the art will 25 understand that the selection of a particular useful promoter depends on the exact cell lines and the other various parameters of the genetic construct to be used to express the accessory molecule ligand gene or the chimeric accessory molecule ligand gene within a 30 particular cell line. In addition, one of ordinary skill in the art will select a promoter which is known to express genes in the target cell at a sufficiently high level to be useful in the present invention.

The genetic vectors and expression vectors of the 35 present invention optionally contain various additional

regulatory sequences including ribosome binding sites which allow the efficient translation of the messenger RNA produced from an expression vector into proteins, the DNA sequence encoding various signals peptides which 5 may be operatively linked to the accessory molecule ligand gene or the chimeric accessory molecule ligand gene. The signal peptide, if present, is expressed as a precursor amino acid which enables improved extracellular secretion of translation fusion 10 polypeptide.

The genetic constructs contemplated by the present invention therefore include various forms of accessory molecule ligand genes described above which are operatively linked to either a promoter sequence or a 15 promoter and enhancer sequence and also operatively linked to a polyadenylation sequence which directs the termination and polyadenylation of messenger RNA. It is also contemplated that the genetic constructs of the present invention will contain other genetic sequences 20 which allow for the efficient replication and expression of that construct within the desired cells. Such sequence may include introns which are derived from native accessory molecule ligand genes or, for example, from a virus gene.

25 The present invention also contemplates gene therapy vectors which are able to directly infect mammalian cells so as to introduce the desired accessory molecule ligand gene or chimeric accessory molecule ligand gene into that cell. These gene therapy vectors 30 are useful for directly infecting cells which have been isolated from an animal or patient, or can be directly introduced into an animal or patient and thereby directly infect the desired cell within that animal or patient.

Many types of gene therapy vectors which are able to successfully transfer genes and cause the expression of desired foreign DNA sequences have been developed and described in the literature. For example, the article 5 entitled "Gene Transfer Vectors for Mammalian Cells" in Current Comm. Mol. Biol., Cold Springs Harbor Laboratory, New York (1987). Further, naked DNA can be physically introduced into eukaryotic cells including human cells by transvection using any number of 10 techniques including calcium phosphate transfection (Berman et al., Proc. Natl. Acad. Sci. USA, 81:7176 (1984)), DEAE-Dextran Transfection, protoplast fusion (Deans et al., Proc. Natl. Acad. Sci. USA, 81:1292 (1984)), electroporation, liposome fusion, polybrene 15 transfection and direct gene transfer by laser micropuncture of the cell membrane. In addition, one of ordinary skill in the art will understand that any technique which is able to successfully introduce the DNA into a cell in such a manner as to allow it to 20 integrate into the genome of a cell and allow the expression of the desired gene would be useful in the present invention.

Specifically, gene therapy vectors which utilize recombinant infectious virus particles for gene delivery 25 have been widely described. See, for example, Brody, S. L. and R. G. Crystal, Ann. N. Y. Acad. Sci., 716:90 (1994); Srivastava, A., Blood. Cells, 20:531 (1994); Jolly, D., Cancer Gene Ther., 1:51 (1994); Russell, S. J., Eur. J. Cancer, 30A:1165 (1994); Yee, J. K., T. 30 Friedmann, and J. C. Burns, Methods Cell Biol., 43 Pt A:99 (1994); Boris-Lawrie, K. A. and H. M. Temin, Curr. Opin. Genet. Dev., 3:102 (1993); Tolstoshev, P., Annu. Rev. Pharmacol. Toxicol., 33:573 (1993); and, Carter, B. J., Curr. Opin. Biotechnol., 3:533 (1992). The present 35 invention contemplates the use of gene therapy vectors

to carry out the desired methodology of the present invention by introducing a gene encoding an accessory molecule ligand gene or a chimeric accessory molecule ligand gene into the cell. Many viral vectors have been defined and used as gene therapy vectors and include virus vectors derived from simian virus 40 (SV40), adenoviruses, adeno-associated viruses, and retroviruses. One of ordinary skill in the art will understand that useful gene therapy vectors are vectors which are able to directly introduce into the target cells the DNA which encodes the accessory molecule ligand and allow that DNA to persist in the cell so as to express the accessory molecule ligand in the desired manner within the cell.

The gene therapy vectors of the present invention are useful for introducing accessory molecule ligand genes into a variety of mammalian cells including human cells. The particular cells infected by the gene therapy vector will depend on the various specifics of the vector and such vectors can be used to introduce the accessory molecule ligand genes of the present invention into hematopoietic or lymphoid stem cells, antigen presenting cells, embryonic stem cells, and other cells which are capable of presenting antigen within the immune system including cells which have CD40 on their surface. Further, such gene therapy vectors are able to introduce a gene encoding an accessory molecule ligand gene into a human neoplastic cell such as a lymphoma, leukemia, AML, CLL, CML, AMML, CMML, breast cancer, lung cancer, ovarian cancer or any tumor capable of acting as antigen presenting cells or cells which can stimulate bystander antigen presenting cells. Further, the contemplated gene therapy vectors may be used to introduce the accessory molecule ligand genes of the present invention into cells which have been engineered

to make those cells capable of presenting antigen to the immune system.

5 III. Cells Containing Genetic Constructs Encoding an Accessory Molecule Ligand or Chimeric Accessory Molecule Ligand

The present invention also contemplates various cells which contain the genetic constructs of the 10 present invention. These cells contain the constructs which encode the accessory molecule ligand gene and thus contain the various genetic elements described in Section II.B. above. These cells may be microbial cells, eukaryotic cells, insect cells, and various 15 mammalian cells including human cells. In preferred embodiments of the present invention, these cells include various neoplastic cells including human neoplastic cells. These neoplastic cells may be of any cell type and include cells of the immune system, and 20 other blood cells. Particularly preferred are any neoplastic cells which may function as an antigen presenting cells within the immune system or which may stimulate bystander antigen presenting cells by expression of a transgenic accessory cell molecule of 25 the present invention. Typically these neoplastic which are able to function to present antigen to the immune system have or have had an accessory molecule, such as the CD40 molecule, on the cell surface. Generally, these cells are naturally capable of presenting antigen 30 to the immune system, but the present invention also contemplates the introduction of accessory molecule ligand genes into a cell which is not naturally able to present antigen to the immune system but which has been genetically engineered to make that cell capable of 35 presenting antigen to the immune system. Typically, these cells include various known cell types such as

monocytes, macrophages, B cells, Langerhans cells, interdigitating cells, follicular dendritic cells or Kupffer cells and the like which have become neoplastic. In addition, the present invention also contemplates 5 cells from various carcinomas, breast, ovarian and lung cancers which contain the genetic constructs described herein. In other preferred embodiments, an accessory molecule ligand gene of the present invention is placed into cells which may be injected into a treatment site 10 such as a tumor bed or joint. For example, the accessory molecule ligand gene of the present invention may be inserted into a fibroblast cell and the accessory molecule ligand expressed on the surface of that cell. The fibroblasts are then injected into the treatment 15 site and cause the desired immuno effect due to the presence of the accessory molecule ligand on the surface of those cells. These cells stimulate other immune cells present in that treatment site (bystander cells). This process then results in the desired effect on the 20 immune system.

IV. Methods Utilizing Genetic Vectors and Constructs Containing an Accessory Molecule Ligand Gene

25 The present invention contemplates methods of altering the immunoreactivity of human cells using a method which includes introducing a gene encoding an accessory molecule ligand gene into the human cells so that the accessory molecule ligand encoded by that gene 30 is expressed on the surface of those cells. The present invention is useful for any human cells which participate in an immune reaction either as a target for the immune system or as part of the immune system which responds to the foreign target. A large variety of 35 methods are contemplated in which the final result is that the accessory molecule ligand gene is introduced

into the desired cells. These methods include ex vivo methods, in vivo methods and various other methods which involve injection of DNA, genetic vectors or gene therapy vectors into the animal or human, including 5 injection directly into the tumor bed present in any animal or human.

Ex vivo methods are contemplated wherein the cells into which the accessory molecule ligand gene is to be introduced are isolated from the animal or patient and 10 then the gene is introduced into those isolated cells using suitable methods. Examples of useful ex vivo methods have been described for example by Raper, S. E., M. Grossman, D. J. Rader, J. G. Thoene, B. J. Clark, D. M. Kolansky, D. W. Muller, and J. M. Wilson, Ann. Surg., 15 223:116 (1996); Lu, L., R. N. Shen, and H. E. Broxmeyer, Crit. Rev. Oncol. Hematol., 22:61 (1996); Koc, O. N., J. A. Allay, K. Lee, B. M. Davis, J. S. Reese, and S. L. Gerson, Semin. Oncol., 23:46 (1996); Fisher, L. J. and J. Ray, Curr. Opin. Neurobiol., 4:735 (1994); and, 20 Goldspiel, B. R., L. Green, and K. A. Calis, Clin. Pharm., 12:488 (1993). D. Dilloo et al., in Blood 90:1927-1933 (1997), describe a method, using CD40L-activated cells, for treating B-acute lymphoblastic leukemia (ALL). They cocultured leukemia cells with 25 fibroblasts infected with a retroviral vector encoding CD40L, then injected the cell mix into mice. Such an approach, if taken in humans, would differ from that contemplated here in that the therapeutic cells are stimulated in vitro, by another cell line expressing the 30 accessory molecule ligand. Schultze, J.L. et al., in Blood 89: 3806-3816 (1997), describe a method for stimulating T-TILs (tumor-infiltrating T cells) cytotoxic for follicular lymphoma (FL) cells by exposing them, in vitro, to FL B cells which were previously 35 cultured with CD40L-expressing fibroblasts. They

propose an adoptive immunotherapy in which T-TILS stimulated in this manner are transfused into patients. This method also requires in vitro stimulation, of the cells to be transfused, with another cell line
5 expressing an accessory molecule.

Following the introduction of the gene, including any optional steps to assure that the accessory molecule ligand gene has been successfully introduced into those isolated cells, the isolated cells are introduced into
10 the patient either at a specific site or directly into the circulation of the patient. In preferred embodiments of the present invention, cell surface markers, including molecules such tumor markers or antigens identify the cells are used to specifically
15 isolate these molecules from the patient. One of ordinary skill in the art will understand that such isolation methods are well known and include such methodologies as fluorescence activated cell sorting (FACS), immunoselection involving a variety of formats
20 including panning, columns and other similar methods.

The present invention also contemplates introducing the accessory molecule ligand gene into the desired cells within the body of an animal or human patient without first removing those cells from the patient.
25 Methods for introducing genes into specific cells in vivo, or within the patient's body are well known and include use of gene therapy vectors and direct injection of various genetic constructs into the animal or patient. Examples of useful methods have been described
30 by Danko, I. and J. A. Wolff, Vaccine, 12:1499 (1994); Raz, E., A. Watanabe, S. M. Baird, R. A. Eisenberg, T. B. Parr, M. Lotz, T. J. Kipps, and D. A. Carson, Proc. Natl. Acad. Sci. U. S. A., 90:4523 (1993); Davis, H. L., R. G. Whalen, and B. A. Demeneix, Hum. Gene Ther., 4:151
35 (1993); Sugaya, S., K. Fujita, A. Kikuchi, H. Ueda, K.

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The present invention also contemplates the direct injection of DNA from a genetic construct which has a 30 promoter and accessory molecule ligand gene followed by a polyadenylation sequence into a patient or animal. Examples of such useful methods have been described by Vile, R. G. and I. R. Hart, Ann. Oncol., 5 Suppl 4:59 (1994). The genetic construct DNA is directly injected 35 into the muscle or other sites of the animal or patient

or directly into the tumor bed of the animal or patient. Alternatively, DNA from a genetic construct containing at least an accessory molecule ligand gene is used and directly injected into the animal.

5 In preferred embodiments of the present invention, the immune reaction or response of a human patient or animal is altered by introducing the accessory molecule ligand gene into cells, including human cells which have an accessory molecule present on the cell surface. Such
10 cells include human cells, human antigen presenting cells and optionally these cells may be neoplastic antigen presenting cells which have the capacity to express the accessory molecule on the surface of the cell or cells which are capable of stimulating. In some
15 embodiments, the amount of accessory molecule present on the surface of the cells into which the accessory molecule ligand gene is to be introduced is very small and such small amounts of the accessory molecule may result from down-regulation of that accessory molecule
20 on the surface of such cells. In some embodiments, the cells into which the accessory molecule ligand gene is introduced have at least low levels of the CD40 molecule present on the cell surface or are derived from cells which did express the CD40 ligand molecule on the cell
25 surface but have reduced or eliminated that expression.

The preferred methods of altering the immunoreactivity of a particular cell are applicable to mammalian cells including human cells. These human cells may include neoplastic human cells such as human
30 lymphomas, leukemias, and other malignancies including breast, lung and ovarian cancers. In some preferred embodiments the cells are normal antigen presenting cells of a human patient such as monocytes, macrophages, B cells, Langerhans cells, interdigitating cells,
35 follicular dendritic cells, Kupffer cells, and other

similar cells. In preferred embodiments, the cells are lymphocytes which acquire altered immunoreactivity when the accessory molecules of the present invention are introduced into those cells. In other preferred 5 embodiments, the cells may be neoplastic or normal cells which are capable of stimulating bystander antigen presenting cells when the accessory molecule ligand genes of the present invention are introduced into these cells. The present invention also contemplates that 10 cells which are not naturally capable of presenting antigen to the immune system may be genetically engineered to introduce the genes encoding the molecules required for antigen presentation, including genes encoding an accessory molecule, and thus allow these 15 cells to act as artificial antigen presenting cells. The accessory molecule ligand gene may then be introduced into these artificial antigen presenting cells. Various tests are well known in the literature to determine whether a particular cell is able to 20 function as an antigen presenting cell, such as cell proliferation or the production of lymphokines and therefore this aspect of the present invention may be easily determined.

In addition to the above normal human cells, the 25 present invention also contemplates introducing the accessory molecule ligand gene into various neoplastic or malignant cells which optionally are antigen presenting cells. Such human neoplastic cells which are contemplated include leukemias, lymphomas, AML, AMML, or 30 CMML, CML, CLL and any neoplastic cell which is capable of stimulating bystander antigen presenting cells when an accessory molecule ligand is introduced into that cell. Also contemplated are neoplastic cells such as a breast, ovarian or lung cancer cell which is capable of 35 or is engineered to act as an antigen presenting cell.

However, the present immunomodulation also applicable to other malignancies not specifically identified and thus would include any tumor of any cell capable of presenting antigen within the animal or human immune system or any cell which is capable of acting as an antigen presenting cell or capable of stimulating bystandant antigen presenting cells after an accessory molecule ligand gene has been introduced into those cells. Generally these antigen presenting cells have accessory molecules on the surface of the cells.

The present methods of altering the immunoreactivity of a human or animal cell contemplate the introduction of an accessory molecule ligand gene into the cells for which altered immunoreactivity is desired. The genes useful in the present invention include the wide range of accessory molecule ligand genes and chimeric accessory molecule ligand genes identified above and in preferred embodiments include at least a portion of the murine CD40 ligand gene. In particularly preferred embodiments, the accessory molecule ligand gene introduced into the cells using the methods of the present invention is selected to correspond to the accessory molecule present on the surface of the cells for which altered immunoreactivity is desired. In one particular application of the present invention, the immunoreactivity of a cell which expresses the CD40 molecule on the cell surface would be accomplished by introducing the gene which encodes the CD40 ligand molecule and more preferably the murine CD40 ligand molecule.

The present invention also contemplates altering the immunoreactivity of human or animal cells by introducing an accessory molecule ligand gene which is a chimeric accessory molecule ligand gene into the cell. The various useful chimeric accessory molecule ligand

genes were identified above and could include a wide variety of molecules and allow the unique properties of those chimeric accessory molecule ligand genes to be utilized to alter the immunoreactivity of the target 5 cells. In preferred embodiments, useful chimeric accessory molecule ligand genes are genes which encode at least a portion of the accessory molecule ligand which is capable of binding the accessory molecule present on the surface of the cells for which altered 10 immunoreactivity is desired.

The methods of the present invention for altering the immunoreactivity contemplate the use of genetic vectors and genetic constructs including gene therapy vectors which encode an accessory molecule ligand and 15 therefore contain an accessory molecule ligand gene. Typically, the genetic vectors and genetic constructs including the gene therapy vectors of the present invention have a promoter which is operatively linked to the accessory molecule ligand gene followed by a 20 polyadenylation sequence. In other embodiments, the only requirement is that the genetic vectors, genetic constructs, and gene therapy vectors of the present invention contain the accessory molecule ligand gene or the chimeric accessory molecule ligand gene.

25

V. Methods of Treating Neoplasia

The present invention also contemplates methods of treating human neoplasia comprising inserting into a 30 human neoplastic cell a gene which encodes an accessory molecule ligand so that the accessory molecule ligand is expressed on the surface of the neoplastic cells. The present invention contemplates treating human neoplasia both in vivo, ex vivo and by directly injecting various 35 DNA molecules containing a gene which encodes an

accessory molecule ligand into the patient. However, at a minimum, the present methods for treating human neoplasia involve inserting the gene encoding the accessory molecule ligand into the neoplastic cells in 5 such a way as to allow those neoplastic cells to express the accessory molecule ligand on the cell surface. The expression of the accessory molecule ligand gene in these neoplastic cells modulates the immune system to cause the neoplasia to be reduced or eliminated.

10 In a preferred method of treating human neoplasia, the method further comprises the steps of first obtaining the human neoplastic cells from a human patient and then inserting into the isolated human neoplastic cells a gene which encodes an accessory 15 molecule ligand so that the accessory molecule ligand is expressed on the surface of the neoplastic cells. The human neoplastic cells having the accessory molecule ligand on the surface of that cell are then infused back into the human patient. One of ordinary skill in the 20 art will understand that numerous methods are applicable for infusing the altered human neoplastic cells containing the gene encoding the accessory molecule ligand back into the patient and that these methods are well known in the art.

25 The contemplated methods of treating human neoplasia are applicable to a wide variety of human neoplasias including lymphomas, leukemias, and other malignancies. In preferred embodiments the human neoplasia is a neoplasia which involves the antigen 30 presenting cells of the human immune system and includes monocytes, macrophages, B cells, Langerhans cells, interdigitating cells, follicular dendritic cells, Kupffer cells, and the like. In other preferred embodiments, the human neoplasia is a leukemia, a 35 lymphoma, AML, AMML, CMML, CML or CLL, lung cancer,

breast cancer, ovarian cancer and other similar neoplasias.

The genetic vectors, genetic constructs and gene therapy vectors useful in the methods of treating human neoplasia of the present invention have been disclosed above and include constructs in which a promoter is operatively linked to the accessory molecule ligand gene or the chimeric accessory molecule ligand gene which is in turn operatively linked to a polyadenylation sequence. The methods of treating human neoplasia contemplate the use of genetic constructs, genetic vectors and gene therapy vectors as described in this specification. In addition, the present invention contemplates the use of DNA which contains at least a gene encoding an accessory molecule ligand gene. This gene may or may not contain a promoter and other regulatory sequences.

In preferred embodiments of the present invention, the cells comprising the human neoplasia are located in at least one defined site termed a tumor bed within the human patient. This tumor bed typically contains the tumor or neoplastic cell together with a number of other cells which are associated with the tumor or neoplastic cells. The present invention contemplates methods of treating such human neoplasia present in a tumor bed by injecting into the tumor bed of the patient, a gene which encodes an accessory molecule ligand so that the accessory molecule ligand is expressed on the surface of the tumor cells thereby causing the cells to participate in an immune reaction. The gene which encodes the accessory molecule ligand may be present as part of a gene therapy vector, genetic construct or genetic vector.

In preferred embodiments, the accessory molecule ligand gene is a chimeric accessory molecule ligand gene

which has at least a portion of the murine CD40 ligand gene is used. In other preferred embodiments, the accessory molecule ligand encoded is capable of binding an accessory molecule present on the human neoplasia to be treated.

The various gene therapy vectors used in the treatment methods of the present invention include vectors which are capable of directly infecting human cells. Such vectors have been described in the literature and are readily adaptable to the methods described in the present invention.

The present invention contemplates the use of any type of gene therapy including the methods of Raper, S.E. et al., Ann. Surg., 223:116 (1996); Lu, L. et al., Crit. Rev. Oncol. Hematol., 22:61 (1996); Koc, O. N. et al., Semin. Oncol., 23:46 (1996); Fisher, L. J. et al., Curr. Opin. Neurobiol., 4:735 (1994); Goldspiel, B. R. et al., Clin. Pharm., 12:488 (1993); Danko, I. et al., Vaccine, 12:1499 (1994); Raz, E. et al., Proc. Natl. Acad. Sci. U.S.A., 90:4523 (1993); Davis, H. L. et al., Hum. Gene Ther., 4:151 (1993); Sugaya, S. et al., Hum. Gene Ther., 7:223 (1996); Prentice, H. et al., J. Mol. Cell Cardiol., 28:133 (1996); Soubrane, C. et al., Eur. J. Cancer, 32A:691 (1996); Kass-Eisler, A. et al., ann. N. Y. Acad. Sci., 772:232 (1995); DeMatteo, R. P. et al., Ann. Surg., 222:229 (1995); Addison, C. L. et al., Proc. Natl. Acad. Sci. U.S.A., 92:8522 (1995); Hengge, U. R. et al., J. Clin. Invest., 97:2911 (1996); Felgner, P. L. et al., Ann. N. Y. Acad. Sci., 772:126 (1995); Furth, P.A., Hybridoma, 14:149 (1995); Yovandich, J. et al., Hum. Gene Ther., 6:603 (1995); Evans, C.H. et al., Hum. Gene Ther., 7:1261.

VI. Methods of Vaccination

The present invention contemplates methods of vaccinating an animal against a predetermined organism comprising administering to that animal a vaccine containing immunogenic animal antigens capable of 5 causing an immune response in that animal against the desired organism together with a vector containing a gene encoding an accessory molecule ligand. The present invention also contemplates methods of vaccinating an animal which include administering the genes which 10 encode the immunogenic antigen capable of causing a desired immune response or altering the immune response to a particular antigen together with a vector containing a gene including the accessory molecule ligand gene. In this particular embodiment, the vector 15 or vectors introduced encode the immunogenic antigens desired and the desired accessory molecule ligand. The present invention also contemplates that the gene or genes encoding the immunogenic peptide or peptides may be present on the same vector as is the gene or genes 20 encoding the accessory molecule ligand.

The vaccination methods of the present invention are general in that they may be used to produce a vaccination against any predetermined organism, such as a virus, a bacteria, a fungus or other organism. In 25 addition, the present vaccination methods may be used to produce an immune response against a neoplastic cell.

In other preferred embodiments, the vaccination methods of the present invention utilize a genetic vector, a genetic construct or a gene therapy vector 30 which contains an accessory molecule ligand gene which is a chimeric accessory molecule ligand gene. That chimeric accessory molecule ligand gene preferably contains at least a portion of the murine CD40 ligand gene. In other preferred embodiments, the vaccination 35 method utilizes a DNA molecule which encodes at the

minimum the accessory molecule ligand gene or a chimeric accessory molecule ligand gene. This particular DNA may or may not include a promoter sequence which directs the expression of the accessory molecule ligand gene.

5 The present invention also contemplates that the vaccination method may utilize a genetic vector which is capable of expressing an accessory molecule ligand within a particular cell or organism together with a vector which is capable of expressing at least a single
10 polypeptide from an andovirus. This andovirus polypeptide may be expressed from the same or different vector which expresses the accessory molecule ligand in that cell. In this particular embodiment, the andovirus polypeptide is also expressed in at least one cell type
15 within the organism and serves to modulate the immune response found in response to this vaccination protocol.

 The present invention also contemplates the introduction of an accessory molecule ligand gene into cells which are present in the joints of patients with
20 rheumatoid arthritis. In preferred embodiments, the accessory molecule ligand gene introduced comprises at least a portion of the Fas ligand gene and upon expression the accessory ligand induces the cell death of cells expressing Fas on the cell surface. This
25 process leads to the reduction of the destructive inflammatory process.

 The following examples are provided to illustrate various aspects of the present invention and do not limit the scope of that invention.
30

VII. Methods of Treating Arthritis

 The present invention also contemplates methods of treating arthritis comprising inserting into a joint,
35 cells which have been transformed with an accessory

molecule, such as the Fas ligand. In preferred embodiments, the expression of that accessory molecule ligand or the stability of that molecule on the surface of the cells has been altered. In these preferred 5 embodiments, the accessory molecule ligand functions in an enhanced manner to aid in the treatment of arthritis within the joint. The present invention contemplates treating human arthritis both in vivo, ex vivo, and by directly injecting various DNA molecules containing 10 genes which encode the useful accessory molecule ligand into the patients. Various useful protocols may be designed to rheumatoid arthritis including those described in the example section below.

The present invention contemplates the treatment of 15 arthritis utilizing accessory molecule ligand genes which may be chimeric accessory molecule ligand genes comprised of portions of that gene being derived from two different accessory molecule ligand genes. In other embodiments, the chimeric accessory molecule ligands may 20 be produced by utilizing domains from the same accessory molecule ligand gene. The resulting chimeric accessory molecule ligands have an altered stability on the surface of cells upon which they are expressed. This altered stability modulates the function of the immune 25 system in the local environment around the cells in which these chimeric accessory molecule ligands are expressed. For example, in certain preferred embodiments, Fas ligand stability is altered on the surface of cells within a joint of a patient suffering 30 from arthritis. This altered stability modulates the immune system and causes the cells to be targeted for apoptosis and thus reducing the immune response within the inflamed joint. In other embodiments, the accessory molecule ligand genes described within are altered such 35 that the resulting accessory molecule ligand has an

altered stability and causes an immunomodulatory effect which can be useful in the treatment of arthritis.

The present invention contemplates in preferred embodiments that chimeric accessory molecule ligands genes be utilized in the treatment of arthritis. These chimeric accessory molecule ligand genes preferably contain at least a portion of the Fas ligand gene Domain IV, which carries the effect or function for Fas ligand. In preferred embodiments, at least in the portion of that domain, is present which allows Fas ligand to have its biologic effects. In other preferred chimeric accessory molecule ligands, those ligands contain domains from other accessory molecule ligand genes of the present invention or from a different domain of the same accessory molecule ligand. Particularly preferred are Fas chimeric accessory molecule ligand genes made up on Domain IV of the human Fas ligand operatively linked with Domain III of the mouse Fas ligand. This particular combination results in more stable Fas ligand and thus, by replacing Domain III of human Fas ligand with Domain III of the mouse ligand, the activity of the human Fas ligand gene is altered.

Alternatively, in other preferred embodiments, the murine Fas ligand gene is used to encode the murine Fas ligand on the surface of cells in place of the human Fas ligand. The murine Fas ligand is more stable than the human Fas ligand and thus, alters the Fas ligand activity in the joint. The resulting alter Fas ligand activity is useful in the treatment of rheumatoid arthritis.

Further preferred embodiments include embodiments in which the effect or function present on Domain IV of the humand Fas ligand is combined with other domains from other accessory molecule ligands. For example, CD70 Domain III is more stable than Domain III of the

human Fas ligand and thus the chimeric accessory molecule ligand made up of Domain III from the human CD70 and Domain IV of the Fas ligand together with other supporting domains would be more stable. The increased 5 stability leads to increase Fas ligand activity. In other preferred embodiments, Domain III of the Fas ligand is replaced with multiple copies of a domain or domains. Such multiple copies of domains include domains made up of two or more copies of other domains 10 such as Domains III or I of the CD70 molecule.

In other preferred embodiments, the present invention contemplates accessory molecule ligand genes, such as Fas ligand genes, in which a cleavage site for matrix-metalloproteinase (MMP), have been removed from 15 the accessory molecule ligand. MMP cleavage and recognition sites, charted in Figure 28, are discussed in Smith, M.M. et al., Journal of Biol. Chem. 270:6440-6449 (95) and Nagase, H., and G.B. Fields, Biopolymers (Peptide Science) 40:399-416 (96). In preferred 20 embodiments, at least one MMP site has been removed from at least Domain III of the Fas ligand gene. The removal of the MMP site from the Fas ligand gene makes the Fas ligand more stable and thus, more effective in the treatment of arthritis.

25 In other preferred embodiments, chimeric accessory molecule ligand genes are comprised of portions of the human Fas ligand gene with other domains from other human accessory molecule ligands or domains from accessory molecules derived from other species. For 30 example, the present invention contemplates the use of domains from CD40 ligand, CD70 ligand, CD30 ligand, TNF-related apoptosis inducing ligand (TRAIL), TNF- α as well as mutants of human Fas ligand and murine Fas ligand. Production of such chimeric accessory molecule ligands 35 is easily accomplished by manipulating and producing

accessory molecule ligand genes which are chimeric and thus has portions derived from at least two different accessory molecule ligand genes.

EXAMPLES

1. Expression of Human and Mouse Accessory Molecule Ligand in Human CLL Cells

5

a. Construction of a Genetic Construct and Gene Therapy Vector Containing a Human and Mouse Accessory Molecule Ligand Gene

10 Either the human accessory molecule ligand gene (human CD40 ligand) or the murine accessory molecule ligand gene (murine CD40 ligand) was constructed utilizing the respective human and murine genes. Each of these genes was cloned in the following manner.

15

i. Murine CD40-L cloning

Total RNA was isolated using the RNA STAT-60 kit (Tel-Test "B" Inc., Friendswood, TX) from 1×10^7 B6 mouse splenocytes that were previously activated for 8 hours with immobilized CD3-specific mAb. cDNA was then synthesized with the Superscript cDNA synthesis kit (Gibco BRL, Grand Island, NY) using oligo-dT primers. The murine CD40 ligand (mCD40-L) gene was then amplified from the cDNA by PCR using the following mCD40-L specific primers. 5'-GTTAAGCTTCAGTCAGCATGATAGAA (SEQ ID NO: 26), 5'-GTTTCTAGATCAGAGTTGAGTAAGCC (SEQ ID NO: 27). The amplified mCD40-L PCR product was subcloned into the HindIII and XbaI sites of the eukaryotic expression vector pcDNA3 (Invitrogen, San Diego, CA). A DNA fragment encompassing the CMV promoter, mCD40-L gene, and polyadenylation signal was released from this plasmid construct after restriction digestion with BglII and XbaI enzymes. This DNA fragment was then subcloned 35 into the shuttle plasmid MCS(SK)pXCX2 (Spessot R, 1989,

Virology 168:378) that was designated mCD40-L pXCX2. This plasmid was used for adenovirus production as described below.

5 ii. Human CD40-L Cloning

A plasmid containing the gene for human CD40-L was used to produce the human CD40-L gene used herein. The sequence of this gene is available and thus this source 10 of the gene was used merely for convenience. See GenBank accession no. X67878. This plasmid was used for PCR amplification of the human CD40-L gene using the specific primers, sense primer 5' CCAAGACTAGTTAACACAGCATGATCGAAA 3' (SEQ ID NO: 28) and 15 antisense primer 5' CCAATGCGGCCGCACTCAGAATTCAACCTG 3' (SEQ ID NO: 29).

These primers contain flanking restriction enzyme sites for subcloning into the eukaryotic expression plasmid pRc/CMV (Invitrogen). The PCR amplified CD40-L 20 fragment was subcloned into the SpeI and NotI sites of pRc/CMV and designated hCD40-L pRc/CMV. A BglII and XhoI fragment encompassing the CMV promoter, hCD40-L gene, and polyadenylation signal was then released from this plasmid and subcloned into the shuttle plasmid 25 MCS(SK)pXCX2 as described above. This plasmid was designated hCD40-L pXCX2. This plasmid was used for adenovirus production as described below.

30 iii. Adenovirus Synthesis

Either mCD40-L pXCX2 or hCD40-L pXCX2 plasmids were co-transfected with pJM17 (Graham and Prevec, 1991, Methods in Molecular Biology, Vol 7) into 293 cells 35 (American Type Culture Collection, Rockville, MD) using the calcium phosphate method (Sambrook, Fritsch, and

Maniatis, 1989, Molecular Cloning, A Laboratory Manual, 2nd edition, chapter 16:33-34). Isolated adenovirus plaques were picked and expanded by again infecting 293 cells. High titer adenovirus preparations were obtained 5 as described (Graham and Prevec, 1991, Methods in Molecular Biology, Vol 7), except for the following modifications. The cesium chloride gradient used for concentrating viral particles was a step gradient, with densities of 1.45 g/cm³ and 1.2 g/cm³. The samples were 10 spun in a SW41 rotor (Beckman, Brea, CA) at 25,000 rpm at 4°C. The viral band was desalted using a Sephadex G25 DNA grade column (Pharmacia, Piscataway, NJ). The isolated virus was stored at 70°C in phosphate buffered saline with 10% glycerol. The virus titer was 15 determined by infecting 293 cells with serial dilutions of the purified adenovirus and counting the number of plaques formed. Viral titers typically ranged from 10¹⁰ to 10¹² plaque forming units/ml (PFU/ml).

20 b. Introduction of a Murine and Human Accessory Molecule Ligand Gene into CLL Cells and HeLa Cells

For adenovirus infection, 10⁶ freshly thawed and 25 washed CLL cells or HeLa cells were suspended in 0.5 to 1 mL of culture medium for culture at 37°C in a 5% CO₂-in-air incubator. Adenovirus was added to the cells at varying multiplicity of infection (MOI), and the infected cells were cultured for 48 hours, unless 30 otherwise stated, before being analyzed for transgene expression.

c. Expression of an Accessory Molecule Ligand Gene in CLL Cells and HeLa Cells

The CLL and HeLa cells which were infected with the adenovirus vector containing either mouse or human CD40 ligand genes prepared in Example 1b. were then stained with commercially available monoclonal antibodies immunospecific for either human or mouse CD40 ligand (Pharmingen, San Diego, CA) using the manufacturer's directions. The CLL and HeLa cells were washed in staining media (SM) consisting of RPMI-1640, 3% fetal calf serum and 0.05% sodium azide and containing propidium iodide and then analyzed on a FACScan (Becton Dickinson, San Jose, CA). Dead cells and debris were excluded from analysis by characteristic forward and side light scatter profiles and propidium iodide staining. Surface antigen expression was measured as the mean fluorescence intensity ratio (MFIR). MFIR equals the mean fluorescence intensity (MFI) of cells stained with a specific FITC-conjugated MoAb, divided by the MFI of cells stained with a control IgG-FITC. This method controls for the nonspecific increases in auto-fluorescence seen in larger, more activated cells.

The histograms, generated for the CLL cells and HeLa cells containing either a genetic vector containing the human CD40 ligand gene or the murine CD40 ligand gene and the appropriate controls, are shown in Figure 3A-3D. The expression of both the murine and human accessory molecule ligand gene (CD40 ligand) in HeLa cells is shown in Figures 3A and 3B, respectively. The expression of the murine and human accessory molecule ligand in CLL cells is shown in Figures 3C and 3D. The expression of an accessory molecule ligand gene in CLL cells and the expression of murine CD40 ligand on the surface of the CLL cells is shown in Figure 3C. The

failure of the human accessory molecule ligand to be expressed on the surface of the CLL cells is shown in Figure 3D.

Figure 8 shows data from an experiment done to 5 examine whether the CD4⁺ T cells of CLL patients could be induced to express the accessory molecule ligand mRNA after CD3 ligation. An ELISA-based quantitative competitive RT-PCR was used to measure CD40 ligand transcript levels. In this experiment, CD40 ligand and 10 RNA transcribed from the CD40 ligand gene in CLL cells are compared with levels of CD40 ligand and RNA made in normal donor cells, after induction by CD3 ligation. For CD3 activation, plate coats of CD3 mAb were made and 15 incubated with plated CLL or normal donor mononuclear cells for the indicated amount of time, after which cells were analyzed for expression of surface antigens or CD154 RNA message levels. CLL or normal donor serum was added to the cells at the beginning of the activation assay for examination of modulation of CD40 20 ligand surface expression.

For quantitative CD154 RT-PCR ELISA, total RNA was extracted and competitor RNA was generated from the insert containing CD40 ligand (CD154) cDNA. Varying amounts of competitor RNA were added to separate wells 25 of isolated total RNA that subsequently were converted into cDNA. CD3 activation, ELISAs and PCR reactions were performed as described in Cantwell, M. et al., Nature Medicine 3:984-989 (1997). Biotinylated PCR products were captured onto microtiter plates (Becton 30 Dickinson, Oxnard, CA) coated with streptavidin (Sigma), and incubated. The plate was treated with NaOH to remove the sense strands and subsequently washed. The DNA was then hybridized with either wild-type gene-specific or competitor-specific oligonucleotides. Using 35 terminal transferase, each probe was labeled with a

molecule of digoxigenin-11-dideoxyUTP (Boehringer Mannheim). The plate was incubated and washed with HYBE buffer and blocking buffer, then peroxidase-conjugated anti-digoxigenin antibody (150 U/ml; Boehringer Mannheim) in blocking buffer was added. TMB (tetramethylbenzidine) and peroxidase (Kirkegaard and Perry Laboratories, Gaithersburg, MD) were added for color development, and optical densities were measured at 450 nm and Deltasoft II (Biometallics, Princeton, NJ) was used for data analysis.

Standard curves plotting the moles of RNA product versus the optical density were made for the standard cDNA reactions. The equations describing these standard curves were then used to calculate the moles of wild-type or competitor DNA present in the unknown PCR reactions based on the optical densities obtained in the ELISA readings. The ratio of the quantity of wild-type DNA to the amount of competitor DNA was then plotted against the known quantity of competitor RNA added in the initial samples. The ratio of 1 was taken for the extrapolation of the amount of unknown moles of target RNA in the sample (a ratio of 1 means the amount of target RNA versus competitor RNA are equal). The molecules of target RNA per CD4 cell was then calculated based on the following formula: [(moles target CD154 RNA) x (6 X 10²³ molecules/mole) x (dilution factor of test RNA)]/(% of CD4 T cells in total cell population).

The upper graph in Figure 8 shows that T cells of patients with CLL do not express detectable CD40 ligand after CD3 ligation. CD40 ligand RNA is produced, but it is not stable. Although both CD40 ligand and CD40 ligand RNA are expressed in normal donor T cells (lower graph), the levels of neither the protein or RNA are stably maintained.

Figure 9 shows a time course for surface expression of CD40 ligand. Expression reached a peak level at 48 hours after infection and persisted at high levels for at least 6 days thereafter. In this experiment, CLL B 5 cells were infected with a gene therapy vector containing an accessory molecule ligand, at a MOI of 1000 at time zero, and then assessed by flow cytometry at various times thereafter. At each time point listed on the abscissa, the proportions of viable CLL B cells 10 that expressed detectable CD154 are indicated by the vertical bars corresponding to the percentage scale depicted on the right-hand ordinate.

- 15 d. Function of the Human and Murine Accessory Molecule Ligands
- 20 i. Induction of CD80 and CD54 on Cells Containing a Gene Therapy Vector Encoding an Accessory Molecule

25 The CLL cells infected with the murine accessory molecule ligand gene prepared in Example 1b. were then cultured in tissue culture plates. The CLL cells were then analyzed using multiparameter FACS analysis to 30 detect induction of CD80 and CD54 expression using fluroescein isothiocyanate-conjugated monoclonal antibodies immunospecific for each of these respective surface antigens. Non-infected CLL cells were used as a control. The cells were subjected to the appropriate 35 FACS analysis and histograms were generated. CD80 mAb was obtained from Dr. Edward Clark and CD54 mAb was purchased from CALTAG Inc. The CD80 was conjugated using standard methods which have been described in Kipps et al., Laboratory Immunology II, 12:237-275 35 (1992).

The results of this analysis are shown in Figure 4A-4D. Figures 4A-4B compare the amount of CD54 expression in CLL cells which have not been transfected (Figure 4A) or CLL cells into which a gene therapy vector containing the murine CD40 ligand gene was introduced (Figure 4B). The shaded graph indicates the isotype control for FACS staining and the open graph indicates the cells stained with the anti-CD54 antibody. These results show that the level of expression of CD54 is increased in CLL cells into which the gene therapy vector containing the murine CD40 ligand was introduced.

Figures 4C and 4D compare the amount of CD80 expression in CLL cells which have not been transfected (Figure 4C) or CLL cells into which a gene therapy vector containing the murine CD40 ligand gene was introduced (Figure 4D). The shaded graph indicates the isotype control for FACS staining and the open graph indicates the cells stained with the anti-CD80 antibody. These results show that the level of expression of CD80 is increased in the CLL cells into which the gene therapy vector containing the murine CD40 ligand was introduced.

In an additional experiment, CLL cells infected with a gene therapy vector containing the murine accessory molecule ligand gene were evaluated by flow cytometry for induced expression of not only CD54 and CD80, but also CD86, CD58, CD70 and CD95. Fluorescein-conjugated mAb specific for human CD54 and CD70 were purchased from CALTAG. Fluorescein-conjugated mAb specific for human CD27, CD58, CD80, CD86, or CD95, and phycoerythrin-conjugated mAb specific for human or mouse CD40 ligand, were obtained from PharMingen. Shaded histograms represent staining of CLL B cells with FITC-conjugated isotype nonspecific mAb. In contrast to uninfected CLL cells (Figure 10, thin-lined histograms),

or Ad-lacZ-infected CLL cells (data similar to that obtained with uninfected cells, but not shown), CLL cells infected with the adenovirus vector encoding the CD40 ligand (CD154) expressed high levels of CD54

5 (Figure 10, top left), CD80 (Figure 10, top middle), CD86 (Figure 10, top right), CD58 (Figure 10, bottom left), CD70 (Figure 10, bottom middle), and CD95 (Figure 10, bottom right). On the other hand, CD40 ligand-CLL (CD154 CLL) expressed significantly lower levels of both

10 surface membrane CD27 (Figure 11A, thick-lined histogram) and soluble CD27 (Figure 11B) than uninfected (Figure 11A, thin-lined histogram) ($P < 0.01$, Bonferroni t-test) or Ad-lacZ-infected CLL cells (data similar to that obtained with uninfected cells, but not shown). In

15 the experiment shown in Figure 11A, the CLL B cells were examined for expression of CD27 via flow cytometry, three days after infection. Shaded histograms represent staining of CLL B cells with FITC-conjugated isotype control mAb. In Figure 11B, cell-free supernatants were

20 collected, after the infection or stimulation of CLL B cells, for 72 hours and tested for the concentration of human CD27 by ELISA. The reduced expression of CD27 (Figure 11B) is similar to that noted for leukemia B cells stimulated via CD40 cross-linking with mAb G28-5

25 presented by CD32-expressing L cells, as described in Rassenti, L.Z. and T.J. Kipps, J. Exp. Med. 185:1435-1445.

30

ii. Allogeneic T Cell Responses to CLL Cells
Into Which a Genetic Therapy Vector
Containing a Murine CD40 Ligand Gene Has
Been Introduced

The ability of CLL cells which have been infected
35 with a gene therapy vector containing the murine CD40

ligand gene to stimulate allogeneic T cells (i.e., from another individual) was analyzed using cell proliferation assays. Briefly, the test cells were co-cultured with the genetic therapy vector containing the 5 lac-Z gene or the murine CD40 ligand gene at a multiplicity of infection of 1,000 in the presence of IL-4 at a concentration of 10 ng/ml. In other samples, the CLL cells were stimulated with MOPC21 (a control IgG) or G28-5 (an anti-CD40 monoclonal antibody) or were 10 preincubated on CD32-L cells and at the same time treated with IL-4. The preincubation with the CD32-L cells together with IL-4 treatment have been shown to be an efficient form of cross-linking the CD40 molecule other than direct gene transfection.

15 After three days of culture at 37°C, these cells were treated with mitomycin C to prevent their proliferation and then used to stimulate allogeneic T cells. Prior to this co-culture, the different aliquots of CLL cells had either been treated with the anti-CD40 20 monoclonal antibody or had been infected with the gene therapy vector containing either the lac-Z or murine CD40 ligand gene at a stimulator ratio of 1:10. After two days of culture at 37°C, interferon gamma (IFN γ) production was measured by ELISA assay. After five days 25 of co-culture at 37°C, the incorporation of 3 H-thymidine into replicating cells was measured after an eight hour pulse label. The results of this assay are shown in Table II below and in Figure 5.

In another experiment, CLL B cells infected with 30 the gene therapy vector containing the CD40 ligand gene were evaluated for their ability to act as stimulator cells in an allogeneic mixed lymphocyte T cell reaction (MLTR). In parallel, the stimulatory capacity of control lac-Z-vector-infected CLL cells and CLL B cells 35 that had been cultured with CD32-L cells and an anti-

CD40 mAb (G28-5) or an isotype control Ig, was also examined as described in Ranheim, E.A. and T.J. Kipps, J. Exp. Med., 177:925-935 (1993), Clark, E.A. and J.A. Ledbetter, Proc. Natl. Acad. Sci. USA, 83:4494-4498 5 (1986), and Banchereau, J. et al., Science 251:70-72 (1991). Effector T cells from a non-related donor were co-cultured with the CLL stimulator cells at an effector to target ratio of 4:1. After 18 h culture at 37°C, over 30% of the allogeneic CD3⁺ cells were found to 10 express the activation-associated antigen CD69 when cultured with CD154-CLL cells (data not shown). In contrast, less than 4% of the T cells expressed CD69 when co-cultured with uninfected or Ad-lacZ-infected CLL cells (data not shown).

15 Two days after the initiation of the MLTR, the concentrations of IFN γ in the culture supernatants were assayed by ELISA. The supernatants of the MLTR stimulated with CLL cells infected with the accessory molecule ligand CD40L (Figure 12A, CD154-CLL) contained 20 significantly higher levels of IFN γ (306 ± 5 ng/ml, $m \pm$ SE, $n = 3$) than that of MLTR cultures stimulated with the anti-CD40 mAb (Figure 12A, α CD40-CLL) (23 ± 3 ng/ml) ($P < 0.05$, Bonferroni t-test). The latter was not significantly different from that of MLTR cultures 25 stimulated with control Ad-lacZ-infected CLL cells (Figure 12A, lacZ-CLL) (43 ± 10 ng/ml) ($P > 0.1$, Bonferroni t-test). The supernatants of effector cells alone, or of MLTR cultures stimulated with uninfected CLL cells (Figure 12A, CLL) or control Ig treated CLL 30 cells (Figure 12A, MOPC-CLL), did not contain detectable amounts of IFN γ (<2 ng/ml). Similarly, none of the leukemia B cell populations produced detectable amounts of IFN γ when cultured alone, without added effector T cells (data not shown).

After 5 days, cell proliferation was assessed by incorporation of ^3H -thymidine. Cultures with isotype control IgG-treated (Figure 12B, MOPC-CLL) or uninfected (Figure 12B, CLL) stimulator cells did not incorporate more ^3H -thymidine than cultures without added leukemia-stimulator cells (Figure 12B, None). Ad-lacZ-infected CLL B cells (Figure 12B, lacZ-CLL) also were unable to stimulate allogeneic T cells to incorporate amounts of ^3H -thymidine that were much greater than that of control cultures. In contrast, anti-CD40-stimulated leukemia cells or CD154-CLL cells each induced significant effector cell proliferation (Figure 12B, α CD40-CLL or CD154-CLL) ($P < 0.05$, Bonferroni t-test). Moreover, the amount of ^3H -thymidine incorporated by cultures stimulated with CD154-CLL cells ($41,004 \pm 761$ cpm ($m \pm SE$), $n = 3$) was significantly greater than that of cultures stimulated with equal numbers of α CD40-CLL cells ($22,935 \pm 1,892$ cpm; $n = 3$) ($P < 0.05$, Bonferroni t test). However, neither of these mitomycin-C-treated leukemia cell populations incorporated ^3H -thymidine when cultured without effector T cells (data not shown). Also, as described for the MLTR between allogeneic T cells and CD40-stimulated CLL cells {6549, 7167, 7168}, allogeneic T cell proliferation in response to CD154-CLL could be inhibited by CTLA-4-Ig or CD11a mAb when added at the initiation of the MLTR, indicating that respective interactions between CD80/CD86 and CD28, or CD54 and CD11a/CD18, contribute to the noted allogeneic T cell reaction (data not shown).

Table IIAllogeneic T cell responses to CLL cells infected with mCD40-L adenovirus

5

	Stimulators	mCD40-L	Human CD80	% positive cells		Allogeneic response (mean±SEM)
				3H-TdR uptake (cpm)	IFN γ production (ng/ml)	
10	None (T cells only)	-	-	3577 ± 821	n.d.*	
	CLL with:					
	No activation	0	1.4	4577 ± 1097	n.d.	
	MOPC21	0	1.0	5259 ± 1788	n.d.	
	G28-5	0	26.7	22935 ± 1892	22.3 ± 1.6	
15	lac-Z adeno	0	4.8	9037 ± 1781	43.2 ± 10.5	
	mCD40-L adeno	17.5	19.7	41004 ± 761	305.7 ± 4.5	

* n.d. - not detectable

20 iii. Stimulation of Gamma Interferon by CLL Cells Containing an Accessory Molecule Ligand Gene

The function of CLL cells containing an accessory molecule ligand gene (mouse CD40 ligand) was analyzed by determining the ability of those cells to activate T lymphocytes. The procedure was performed as follows: allogeneic T lymphocytes from a healthy donor (greater than 90% CD3+) were purified using magnetic beads and monoclonal antibodies specific for the CD14 and CD19 antigen. These allogeneic T lymphocytes then were cultured together with MMC-treated CLL cells which were infected with the accessory molecule ligand gene (murine CD40 ligand) or the lac-Z gene. This co-culture was performed in RPMI-1640 medium containing 10% fetal calf serum. After culture for 24 hours, the cells were

collected and analyzed to determine the expression of the antigen CD69 on the T lymphocytes using a standard FACS sorting protocol. The cell culture supernatants were collected after two days in culture and tested to 5 determine the concentration of human interferon gamma using an ELISA assay. A portion of the CLL cells containing an accessory molecule ligand gene (murine CD40 ligand) and a portion of the cells containing the adenovirus expressing the lac-Z were cultured in the 10 presence of human interleukin 4 IL-4 (5 ng/mL). The production of interferon gamma by allogeneic T lymphocytes in the presence of this amount of human interleukin 4 was also analyzed. The results from these analyses are shown in Figure 6.

15 As can be seen, the human CLL cells containing the accessory molecule ligand gene (murine CD40) produced substantially higher concentrations of interferon gamma in the cell culture supernatant when compared to CLL cells which contained the lac-Z gene. The increased 20 production of interferon gamma (IFN γ) by T lymphocytes exposed to CLL cells containing the accessory molecule ligand gene indicates that these CLL cells containing the accessory molecule ligand genes were effective in producing an enhanced immune response.

25

iv. Stimulation of Allogeneic T Cells Pre-
Exposed to Non-Modified CLL B Cells
Containing an Accessory Molecule Ligand
Gene

30

Prior studies indicated that antigen presentation to T cells, in the absence of the signals derived from costimulatory molecules such as CD28, can lead to specific T cell clonal anergy. For this reason, 35 allogeneic T cells that had previously been cultured,

with non-modified CLL B cells lacking expression of CD80 and other immune accessory molecules, were tested for their ability to respond to CLL cells containing the CD40 ligand gene. Allogeneic effector cells did not

5 incorporate more ^3H -thymidine in response to non-modified CLL cells (Figure 12C, CLL), or control CLL cells infected with Ad-lacZ (Figure 12C, lacZ-CLL), than when they were cultured alone (Figure 12C, None). In contrast, even after prior co-culture with non-modified

10 CLL B cells, allogeneic effector cells could still be induced to proliferate (Figure 12C, CD154-CLL) or to produce IFN γ (Figure 12D, CD154 CLL) in response to cells expressing an accessory molecule ligand. Although modest amounts of IFN γ were detected in the supernatants

15 of such secondary cultures when Ad-lacZ-infected leukemia cells were used as stimulator cells (Figure 12D, lacZ-CLL), this level was significantly lower than that noted for secondary cultures with Ad-CD40-ligand-infected CLL cells (Figure 12D, CD154-CLL) ($P < 0.05$, Bonferroni t-test). Similarly, the supernatants of the leukemia cells alone (data not shown), and the effector cells alone (Figure 12D, None), of the MLTR cultures stimulated with uninfected CLL cells (Figure 12D, CLL), contained negligible amounts of IFN γ (<2 ng/ml). These

20 results indicate that allogeneic effector cells cultured with nonmodified CLL B cells are not precluded from responding to CLL B cells infected with a gene therapy vector containing the accessory molecule ligand gene.

v. Autologous T Cell Responses to CLL Cells Into Which a Gene Therapy Vector Encoding a Murine Accessory Molecule Ligand Gene Has Been Introduced

5

T cells isolated from the blood of CLL patients were examined for their ability to respond in vitro to autologous CLL B cells containing a gene therapy vector which encodes the murine accessory molecule, CD40 ligand. T cells were isolated to >95% purity, and then co-cultured with mitomycin-C-treated autologous leukemia cells in serum-free AIM-V medium supplemented with exogenous interleukin-2 at 25 U/ml. Modest ^3H -thymidine incorporation (<10,000 cpm) was detected in cultures without added stimulator cells, secondary in part to the exogenous IL-2 (Figure 13A, and data not shown). The level of T cell proliferation, however, did not increase in response to uninfected CLL cells (Figure 13A, CLL) or Ad-lacZ-infected CLL cells (Figure 13A, lacZ-CLL). In contrast, CLL cells infected with a gene therapy vector containing the accessory molecule ligand (Figure 13A, CD154-CLL) induced autologous T cells to incorporate significantly more ^3H -thymidine ($17, 368 \pm 1,093$ cpm, n=3) than any of the control cultures ($P < 0.05$, Bonferroni t-test). Furthermore, the MLTR stimulated with CLL cells infected with a vector encoding an accessory molecule ligand (CD40L) also generated significantly more IFN γ (165 ± 3 ng/ml, n=3) than any of the other cultures (Figure 13B) ($P < 0.05$, Bonferroni t-test).

The T cells were harvested after 5 days from the autologous MLTR and assessed for CTL activity against autologous CLL B cells. T cells co-cultured with autologous CD40-ligand-CLL cells developed CTL activity for non-modified CLL B cells, effecting 40.1% lysis (\pm

2.3%) at an E:T ratio of 2:1 (Figure 13C, CD154). However, such T cells did not develop detectable CTL activity for the same target cells in the control reactions, when co-cultured with uninfected or Ad-lacZ-
5 infected CLL cells (Figure 13C).

vi. Specificity of CTL Stimulated by Autologous CD40-Ligand-CLL B Cells for Allogeneic CLL B Cells

10

Effector cells stimulated with autologous CD40-ligand-CLL were evaluated for their ability to secrete IFN γ or manifest CTL activity against allogeneic CLL B cells (Figure 14). After 5 days of autologous MLTR with
15 CD154-CLL or lacZ-CLL, T cells were isolated by Ficoll density gradient centrifugation, washed extensively, and then cultured in media for 24 h. Washed T cells were mixed with autologous ("Auto CLL", solid bar) or allogeneic ("Allo-1 CLL" or "Allo-2 CLL", shaded or
20 hatched bars) target CLL B cells. T cells stimulated in the autologous MLTR with CD40-ligand-CLL cells, but not with lacZ-CLL cells, produced significantly more IFN γ in response to secondary culture with non-modified autologous CLL B cells than with allogeneic CLL B cells
25 (Figure 14A) ($P < 0.05$, Bonferroni t-test). Furthermore, T cells stimulated with CD40-ligand-CLL cells, but not with lacZ-CLL cells, were cytotoxic for autologous CLL cells, but not allogeneic CLL cells (Figure 14B). Similar results were obtained with the autologous MLTR-
30 activated T cells of the allogeneic donor, again demonstrating specific cytotoxicity for autologous CLL B cells (data not shown). Finally, W6/32, a mAb to class I major histocompatibility complex (MHC I) antigens could significantly inhibit the cytotoxicity of T cells
35 stimulated with CD40-ligand-CLL cells for autologous CLL

B cells (Figure 14C, α HLA-class I)) ($P < 0.05$, Bonferroni t-test). Such inhibition was not observed with mAb specific for MHC class II antigen (Figure 14C, α HLA-DP), mAb specific for the Fas-ligand (Figure 14C, α FasL), or an isotype control mAb of irrelevant specificity (Figure 14C, MOPC-21). Collectively, these studies indicate that Ad-CD40-ligand-infected CLL cells can induce an autologous anti-leukemia cellular immune response in vitro, leading to the generation of MHC-class I-restricted CTL specific for autologous non-modified leukemia B cells.

15 e. Transactivation of Non-Infected Bystander Leukemia B Cells by Ad-CD40L CLL Cells

To address whether the changes in tumor marker expression (described in section 1di.) resulted from intracellular versus intercellular stimulation, the effect of culture density on the induced expression of CD54 and CD80 following infection with adenovirus gene therapy vector encoding the accessory molecule ligand (CD40L, or CD154) was examined. After infection, CLL cells were cultured at standard high density (e.g. 1×10^6 cells/ml) or low density (e.g. 2×10^5 cells/ml) for 20 3 days at 37° C. Cells plated at high density contained homotypic aggregates, whereas cells plated at low density remained evenly dispersed and without substantial cell-cell contact (data not shown). Despite expressing similar levels of heterologous CD154, CD154-25 CLL B cells cultured at high density were induced to express higher levels of CD54 and CD80 than CD154-CLL cells cultured at low density (Figure 15A). The stimulation achieved at high density could be inhibited by culturing the cells with a hamster anti-mouse CD154 30 mAb capable of blocking CD40<->CD154 interactions 35

(Figure 15B, α CD154 Ab). Collectively, these studies indicate that CD154-CLL cells can activate each other in *trans* and that surface expression of CD154 is necessary for optimal leukemia cell stimulation.

5 In addition, Ad-CD154-infected, uninfected, Ad-lacZ-infected, or G28-5-stimulated CLL cells were labeled with a green-fluorescence dye to examine whether CD154-CLL could stimulate non-infected bystander leukemia cells. Dye-labeled cells were used as
10 stimulator cells for equal numbers of non-labeled syngeneic CLL B cells. After 2 days' culture, stimulator cells cultured by themselves retained the green-fluorescence dye, allowing such cells to be distinguished from non-labeled CLL cells by flow
15 cytometry. Bystander (green-fluorescence-negative) CD19⁺ CLL B cells were induced to express CD54 (Figure 15C, right histogram) or CD86 (Figure 15D, right histogram) when co-cultured with Ad-CD154-infected leukemia B cells, but not with mock infected CLL cells (Figures 15C
20 and 15D, left histograms), G28-5-stimulated CLL cells, or Ad-lacZ-infected CLL cells (data not shown). As expected, these bystander (green-fluorescence-negative) CLL cells also were negative for heterologous CD154.

25 f. Treatment of Leukemia with Gene Therapy
Vectors Encoding an Accessory Molecule Ligand

Figure 24 shows an outline for a clinical trial for testing treatment of B cell CLL with adenovirus gene
30 therapy vectors encoding modified CD40 ligand. Leukemia cells harvested by pheresis are infected with replication-defective vectors that encode the modified CD40 ligand. Following expression of this protein, the cells will be administered back to the patient for the
35 purpose of stimulating a host anti-leukemia-cell immune

response. This strategy is far superior to one that uses gene therapy to affect expression of only one immune stimulatory molecule on the leukemia cell surface. Indeed, this strategy results in the leukemia 5 cells expressing an array of immune-stimulatory accessory molecules and cytokines, as well as a molecule that can affect the same changes in leukemia cells of the patient that were never harvested.

10

2. Expression of Chimeric Accessory Molecule Ligand Genes

The chimeric accessory molecule ligand genes 15 described below are prepared using standard techniques as described herein.

a. Preparation of Chimeric Accessory Molecule Ligand Genes Utilizing Domains from Two Different Accessory Molecule Genes

The human CD40 ligand gene was isolated from RNA prepared from T cells which had been activated by an anti-CD3 monoclonal antibody using 5' and 3' primers 25 together with well known PCR methods. Chimeric accessory molecule genes of human CD40 ligand and murine CD40 ligand are constructed from the newly cloned human CD40 ligand gene and mouse CD40 ligand gene described herein as SEQ ID NO: 2. The transmembrane and 30 cytoplasmic domains of human CD40 ligand genes are exchanged with those of the murine CD40 ligand gene and designated H(Ex)-M(Tm-Cy) CD40 ligand. These chimeric accessory molecule ligand genes are produced using the gene conversion technique described as SOEN which has 35 been previously described by Horton, Mol. Biotechnol.,

3:93 (1995). A diagram depicting the chimeric accessory molecule ligand genes which are produced is shown in Figure 4. The nucleotide sequences of each of these respective chimeric accessory molecule ligand genes is 5 designated SEQ ID NOS: 3-7 as indicated in the Table below.

Table III

10

	<u>Chimeric Accessory Molecule Ligand Gene</u>	<u>SEQ ID NO:</u>
--	--	-------------------

	HuIC/HuTM/MuEX CD40-Ligand	SEQ ID NO: 3
	HuIC/MuTM/HuEX CD40-Ligand	SEQ ID NO: 4
15	HuIC/MuTM/MuEX CD40-Ligand	SEQ ID NO: 5
	MuIC/HuTM/HuEX CD40-Ligand	SEQ ID NO: 6
	MuIC/MuTM/HuEX CD40-Ligand	SEQ ID NO: 7

Adenovirus vectors encoding each of the chimeric 20 accessory molecules shown in Figure 2 are constructed using the methods described in Example 1. Each of these constructs are then transfected into either HeLa cells or CLL cells according to the methods of Example 1.

25

b. Expression of Chimeric Accessory Molecule Ligands on CLL and HeLa Cells

The expression of each of the chimeric accessory molecule ligand genes constructed above is analyzed by 30 using FACS analysis as specified in Example 1. The appropriate monoclonal antibody immunospecific for the external domain of either human or mouse CD40 ligand is selected and used to determine the level of expression of the chimeric accessory molecules on the surface of 35 these cells. After appropriate analysis and preparation of appropriate histograms, the expression of chimeric accessory molecules containing at least a portion of the murine CD40 ligand gene is confirmed.

c. Function of Chimeric Accessory Molecule Ligands

CLL cells are infected with various MOI of the
5 mCD40L adenovirus and then cultured in 48 or 24 well
tissue culture plates for various times after infection
(48, 72, and 96 hours). The CD19⁺ B cells are then
analyzed by multiparameter FACS analysis for induction
of CD80 and CD54 expression using fluroescein
10 isothiocyanate-conjugated mAb specific for each
respective surface antigen as described in Example 1.
Increased amounts of CD54 and CD80 are found on cells
which have the chimeric accessory molecules containing
the domain or domains derived from the mouse CD40 ligand
15 gene.

Further analysis of the cells containing the
chimeric accessory molecule genes is carried out
according to Example 1(d). The cells containing the
20 chimeric accessory molecule genes which contain the
domains derived from the murine CD40 ligand gene are
able to stimulate the production of gamma interferon and
T cell proliferation.

d. Expression of Chimeric Accessory Molecule Genes Which Contain Proximal Extracellular Domains from Two Different Accessory Molecules from the Same Species

A chimeric accessory molecule ligand gene is
30 prepared which contains the proximal extracellular
domain from the human CD70 gene (Domain III) with the
remainder of the domains derived from the human CD40
ligand gene. This gene is prepared using standard
biologic techniques as previously described herein.
35 This chimeric accessory molecule ligand gene has the DNA

sequence shown as SEQ ID NO: 19. A different chimeric accessory molecule ligand gene is prepared which contains the proximal extracellular domain from the murine CD40 ligand gene with the remainder of the 5 domains derived from the human CD40 ligand gene. This gene is prepared using standard techniques as previously described herein. This chimeric accessory molecule ligand gene has the DNA sequence shown as SEQ ID NO: 20.

The chimeric accessory molecule genes shown as SEQ 10 ID NOS: 19 and 20 are inserted into the appropriate vectors as described in Example 1 and introduced into human neoplastic cells. The expression of that chimeric accessory molecule gene in the cells is determined as was described in Example 1.

15 The chimeric accessory molecule encoded by each of these chimeric accessory molecule genes is found on the surface of the human neoplastic cells using the FACS analysis described in Example 1. Increased amounts of CD54 and CD80 are found on the cells containing the 20 chimeric accessory molecule genes using the techniques described in Example 1. The cells containing the chimeric accessory molecule gene are able to stimulate the production of gamma interferon and T cell proliferation as described and assayed according to 25 Example 1.

3. Augmentation of Vaccination Using Vectors Encoding Accessory Molecules

30 The following procedures were used to demonstrate the augmentation of a vaccination protocol using a gene therapy vector encoding an accessory molecule.

a. Augmentation of the Antibody Response in Mice Co-Injected with an Accessory Molecule Gene Therapy Vector and placZ

5 Three different gene therapy constructs were prepared using standard techniques including those techniques described herein. The first was a control gene therapy vector, pcDNA3, which did not contain any gene. The second, placZ, contained the Lac-Z gene which
10 encoded β-galactosidase (β-gal). The third, p-mCD40L, contained the murine CD40 ligand gene described in Example 1.

Prior to any immunizations, serum was isolated from 6-8 week old BALB/c-mice to determine the amount of any initial antibodies to β-galactosidase. Each animal was injected i.m. with 100 micrograms of plasmid DNA per injection. Four separate injections were given at one week intervals.

Prior to the third injection, the animals were bled
20 to monitor the early antibody response to β-gal. One week after the final injection of plasmid DNA, the animals were bled to monitor the late antibody response to beta-galactosidase. To test the sensitivity of the assay, known amounts of anti-β-gal antibodies isolated
25 from an anti-β-gal antiserum were tested in parallel.

Serum dilutions of 1:40, 1:200, or 1:1000 were tested in an ELISA for anti-β-gal antibodies. For this, polystyrene microtiter ELISA plates were coated with β-gal at 10 microgram/ml in phosphate buffered saline.
30 The plates were washed thrice with blocking buffer containing 1% bovine serum albumin (BSA), 0.2% Tween 20 in borate buffered saline (BBS) (0.1M borate, 0.2M NaCl, pH 8.2). 50 microliters of diluted serum were added to separate wells. After at least 1 hour at room
35 temperature, the plates were washed thrice with blocking

buffer and then allowed to react with alkaline phosphatase-conjugated goat anti-mouse IgG antibody. One hour later, the plates again were washed four times with blocking buffer and incubated with 25 ml of TMB peroxidase substrate (Kirkegaard & Perry, Gaithersburg, MD). The absorbance at 405 nm of each well was measured using a microplate reader (Molecular devices, Menlo Park, CA). The higher the O.D. reading, the greater the amount of specific antibody in the sample.

The data for each of two experiments are provided in Tables IV and V which follow on separate sheets. The results are summarized in Tables VI and VII collating the data from the two experiments is provided as well. On the summary page n stands for the number of animals in each of the four groups. S.D. stands for standard deviation and Avg. is the average O.D. reading for all the animals in a particular group.

The results of Group 4 demonstrate that the use of a gene therapy vector encoding an accessory molecule ligand (CD40L) enhances the immunization against β -gal encoded by a genetic or gene therapy vector. The average O.D. reading of the 1:40 dilution of the sera from animals of this group is significantly higher than that of groups 1, 2, and 3 ($P < 0.05$, Bonferroni t tests, see Table VII).

Data from an additional experiment further reinforce the finding that the gene therapy vector encoding an accessory molecule ligand enhances immunization against β -gal (Figure 16). Here, pCD40L and placZ were co-injected into skeletal muscle, to test for enhancement of the immune response to placZ, a pcDNA3-based vector encoding *E. coli* β -galactosidase. The relative anti- β -gal Ab activities were determined via ELISA. As expected, mice injected with either the non-modified pcDNA3 vector or pCD40L alone did not

produce detectable antibodies to β -gal (Figure 16A). Mice were injected with either 100 μ g pcDNA3 (checkered bar), 50 μ g pcDNA3 + 50 μ g pCD40L (lined bar), 50 μ g pcDNA3 + 50 μ g placZ (striped bar), or 50 μ g pCD40L + 50 μ g placZ (solid bar). On the other hand, mice that received placZ and pcDNA3 developed detectable anti- β -gal antibodies one week after the fourth and final injection, at d28. Mice that received placZ and pCD40L developed higher titers of anti- β -gal antibodies than mice injected with placZ and pcDNA3. Figure 16B, ELISA analyses of serial dilutions of sera collected at d28, shows that mice co-injected with placZ and pCD40L had an eight-fold higher mean titer of anti- β -gal antibodies at d28 than mice treated with placZ + pcDNA3.

15

i. Immunoglobulin Subclass Production Stimulated by Accessory Molecule Vector Co-Injection

20 Despite enhancing the titer of the anti- β -gal antibody response, the subclass of anti- β -gal IgG induced by injection of placZ was not altered by the co-injection of pCD40L. IgG_{2a} anti- β -gal antibodies predominated over IgG₁ subclass antibodies in the sera of 25 mice injected with either placZ and pcDNA3 or placZ and pCD40L (Figure 17). Also depicted are the ELISA O.D. measurements of anti- β -gal IgG₁ and anti- β -gal IgG_{2a} present in the pre-immune sera (striped bar) or post-immune sera (solid bar), collected at d28 of each group 30 of mice, injected as indicated on the abscissa. In contrast, BALB/c mice injected with β -gal protein developed predominantly IgG₁ anti- β -gal antibodies, and no detectable IgG_{2a} anti- β -gal antibodies.

ii. Augmentation of Vaccination by Accessory Molecule Vector Requires Co-Injection with placZ at the Same Site

5 The adjuvant effect of the pCD40L plasmid on the anti- β -gal antibody response was noted only when it was injected into the same site as placZ (Figure 18). Groups of BALB/c mice (n=4) received intramuscular injections of placZ and pCD40L together at the same
10 site, or as simultaneous separate injections at distal sites (right and left hind leg quadriceps). A control group received intramuscular injections of placZ and pcDNA3 at the same site. Animals were bled at d28 and the sera tested for anti- β -gal Ab at different
15 dilutions, as indicated on the abscissa. The graph illustrates a representative experiment depicting the mean O.D. at 405 nm of replicate wells of each of the serum samples for each group, at a 1:40, 1:200, or 1:1000 dilution. Animals injected simultaneously with
20 placZ and pCD40L, but at different sites, did not develop detectable anti- β -gal antibodies until d28. Moreover, the anti- β -gal antibody titers of the sera from such animals at d28 were similar to that of mice that received placZ and pcDNA3, and significantly less
25 than that of animals that received placZ and pCD40L together at the same site.

30 iii. Augmentation of Vaccination When Accessory Molecule Vector and placZ are Co-Injected into Dermis

The pCD40L plasmid also enhanced the anti- β -gal antibody response to placZ when injected into the dermis. In the experiment shown in Figure 19, mice
35 received intradermal injections, near the base of the

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tail, with either 50 µg pcDNA3 (checkered bar), 25 µg pcDNA3 + 25 µg pCD40L (lined bar), 25 µg pcDNA3 + 25 µg placZ (striped bar), or 25 µg pCD40L + 25 µg placZ (solid bar). Injections, bleeds and ELISA analyses were

5 performed as in Figure 16A. The checkered bar and lined bar groups each consisted of 8 mice while the striped bar and solid bar groups each consisted of 12 mice. The height of each bar represents the mean O.D. of sera at a 1:40 dilution of each group ± S.E. A statistical

10 analysis of the data indicated that the striped bar and solid bar groups are independent ($P < .05$). As observed with intramuscular injection, mice co-injected with placZ and pCD40L developed detectable serum anti- β -gal antibodies one week following the second injection

15 (d14), and two weeks earlier than mice injected with placZ and pcDNA3. Moreover, these animals also had an eight-fold higher mean titer of anti- β -gal antibodies than mice of the placZ-injected group at d28. Mice injected with either the non-modified pcDNA3 vector or

20 pCD40L alone did not produce detectable antibodies to β -gal.

b. Augmentation of the CTL Response in Mice Co-Injected with an Accessory Molecule Gene Therapy Vector and placZ

25 The ability of pCD40L to enhance induction, by placZ, of CTL specific for syngeneic β -gal-expressing target cells was tested. BALB/c mice co-injected with pCD40L and placZ into skeletal muscle (Figure 20A) or dermis (Figure 20B) generated greater numbers of CTL specific for P13.2, a placZ transfected P815 cell line, than mice co-injected with placZ and pcDNA3. At a 5:1 effector:target ratio, the splenocyte effector cells

30 from mice that received intramuscular injections of

35

placZ and pCD40L achieved greater than 20% specific lysis of P13.2. In contrast, when splenocytes of mice that received the control injection with placZ and pcDNA3 were used, a 9-fold greater ratio of effector to target cells was required to achieve this level of specific lysis. Similarly, the splenocyte effector cells from mice that received intradermal injections of placZ and pCD40L killed more than 50% of the P13.2 cells at effector:target ratios of 4:1. To achieve comparable levels of specific lysis required eight-fold higher effector:target ratios using splenocytes from mice that received intradermal injections of placZ and pcDNA3. Nevertheless, the splenocytes of mice co-injected with pCD40L and placZ did not have greater non-specific CTL activity for P815 cells than that of mice that received placZ along with pcDNA3 (Figure 20). As expected, the splenocytes from mice that received injections of pcDNA3 alone, or pcDNA3 and pCD40L, did not mediate specific lysis of P13.2 or P815 cells.

20

Table IV

Experiment #1

Injections of plasmid DNA i.m.: 4/3/96; 4/10/96; 4/17/96; 4/24/96

ELISA for anti-beta galactosidase

5	antibodies:	Group	Dilution of Pre-Bleed (4/3)			Dilution of Bleed (4/17)		
			Animal	1/140	1/200	1/1000	1/140	1/200
			1	0.09	0.11	0.09	0.06	0.06
10	pcDNA3 (p-control, 100 mcg) (Control vector)		2	0.11	0.09	0.09	0.07	0.07
			3	0.12	0.11	0.10	0.09	0.09
			4	0.11	0.10	0.10	0.08	0.11
			Avg.	0.11	0.11	0.11	0.11	0.11
			S.D.	0.01	0.01	0.01	0.01	0.02
15	p-lacZ (50 mcg)		5	0.13	0.10	0.10	0.07	0.11
	+		6	0.10	0.11	0.10	0.07	0.06
	p-Control (50 mcg)		7	0.19	0.10	0.18	0.07	0.07
			8	0.10	0.09	0.10	0.08	0.07
			Avg.	0.13	0.10	0.12	0.07	0.08
			S.D.	0.04	0.01	0.04	0.01	0.02
20	p-lacZ (50 mcg)		27	0.06	0.06	0.06	0.13	0.11
	+		18	0.06	0.06	0.06	0.27	0.13
	pRcCMV-mCD40L (p-mCD40L, 50 mcg)		19	0.06	0.06	0.06	0.23	0.19
			20	0.06	0.06	0.06	0.23	0.19
25			Avg.	0.06	0.06	0.06	0.74	0.47
			S.D.	0.00	0.00	0.00	1.06	0.66

Table V

Experiment #2 Injections of plasmid DNA i.m.: 6/5/96; 6/12/96; 6/19/96; 6/26/96

Dilutions of sera for anti-beta

	galactosidase antibodies:	Group	Dilution of Pre-Bleed (6/5)			Dilution of Bleed (7/1)		
			1/140	1/200	1/1000	1/140	1/200	1/1
5	p-Control (50 mcg)	9	0.02	0.02	0.06	0.04	0.01	
		10	0.06	0.02	0.10	0.02	0.02	
		11	0.02	0.02	0.07	0.03	0.01	
		12	0.06	0.03	0.05	0.18	0.04	
10	p-mCD40L (50 mcg)	Avg.	0.04	0.04	0.04	0.04	0.04	
		S.D.	0.02	0.01	0.02	0.07	0.01	
15	p-lacZ (50 mcg)	5	0.02	0.03	0.02	0.06	0.04	
		6	0.03	0.02	0.03	0.14	0.03	
20	p-Control (50 mcg)	7	0.56	0.13	0.06	0.29	0.06	
		8	0.01	0.02	0.05	0.06	0.02	
		Avg.	0.15	0.05	0.04	0.13	0.04	
		S.D.	0.27	0.05	0.02	0.11	0.02	
25	p-lacZ (50 mcg)	13	0.23	0.06	0.05	0.28	0.07	
		14	0.02	0.02	0.03	0.04	0.02	
		15	0.02	0.02	0.02	0.89	0.21	
		16	0.05	0.04	0.02	0.11	0.04	
		Avg.	0.08	0.04	0.03	0.33	0.08	
		S.D.	0.10	0.02	0.02	0.39	0.09	

Table VI

Summary

			Pre-Immune @ beta-gal			Early @ beta-ga		
			1/140 1/200 1/1000			1/140 1/200 1/1		
			Avg.	0.11	0.11	0.11	0.11	0.11
5	1)	p-Control (n = 4)	S.D.	0.01	0.01	0.01	0.01	0.02
10	2)	p-mCD40L + p-Control (n = 4)	Avg.	0.04	0.04	0.04	0.04	0.04
			S.D.	0.02	0.01	0.02	0.07	0.01
15	3)	p-lacZ + p-Control (n = 8)	Avg.	0.11	0.04	0.04	0.11	0.03
			S.D.	0.22	0.04	0.01	0.09	0.02
20	4)	p-lacZ + p-mCD40L (n = 8)	Avg.	0.11	0.04	0.03	0.25	0.06
			S.D.	0.10	0.02	0.01	0.32	0.07
		Anti-beta-galactosidase standard:	67 ng	22ng	7.4ng	2.5ng	.82ng	.27ng
	O.D.		3.01	2.98	2.05	1.10	0.52	0.26
			3.14	3.14	2.25	1.20	0.56	0.26

Table VII

BONFERRONI t-TESTS

	Comparison	Difference of means	t	P<.05
5	4 vs 2:	2.06 - 0.04 = 2.02	3.782	Yes
	4 vs 1:	2.06 - 0.11 = 1.95	3.651	Yes
	4 vs 3:	2.06 - 0.61 = 1.45	3.325	Yes
	3 vs 2:	0.61 - 0.04 = 0.57	1.067	No
10	3 vs 1:	0.61 - 0.11 = 0.50	Do not test	
	1 vs 2:	0.11 - 0.04 = 0.07	Do not test	

Degrees of freedom: 20

15

ONE WAY ANALYSIS OF VARIANCE

	Group	N	Mean	Std Dev	SEM
20	1	4	0.11	0.01	0.00
	2	4	0.04	0.04	0.02
	3	8	0.61	1.11	0.39
	4	8	2.06	0.97	0.34
	5	4	1.51	0.77	0.38
	6	4	1.14	0.53	0.26
25	7	4	0.83	0.43	0.22

ONE WAY ANALYSIS OF VARIANCE

	Source of Variation	SS	DF	Variance Est (MS)
30	Between Groups	18.29	6	3.05
	Within Groups	18.39	29	0.63
	Total	36.69	35	

$$35 \quad F = \frac{s^2_{\text{bet}}}{s^2_{\text{wit}}} = \frac{\text{MS}_{\text{bet}}}{\text{MS}_{\text{wit}}} = \frac{3.05}{0.63} = 4.81 \quad P = 0.002$$

4. Treatment of Neoplasia Using a Gene Therapy Vector Containing an Accessory Molecule Gene or Chimeric Accessory Molecule Gene

5 a. Treatment of Neoplasia in Mice

The treatment of a neoplasia in a mouse model system has been demonstrated using the genes encoding accessory molecule ligands of the present invention.

- 10 Gene therapy vectors containing an accessory molecule ligand gene (murine CD40 ligand) were prepared as has been previously described in the above examples. These gene therapy vectors were used to introduce that accessory molecule ligand gene into neoplastic cells,
- 15 Line1 cells, from a tumor which originated in BALB/c mice. The accessory molecules were introduced into the neoplastic cells according to the above examples. The expression of the accessory molecule ligand on the surface of these neoplastic cells was confirmed using
- 20 flow cytometry as has been described in the above examples.

The effectiveness of the accessory molecule ligand genes for treating neoplasia was shown as follows.

- Female BALB/c mice (6-8 weeks old) were injected i.p. 25 with 1.0×10^5 irradiated Line1 neoplastic cells. The neoplastic Line1 cells are derived from a spontaneous lung adenocarcinoma in a BALB/c mouse. This neoplastic cell has been described by Blieden et al., Int. J. Cancer Supp., 6:82 (1991). Other female BALB/c mice 30 were injected i.p. with 1.0×10^5 irradiated Line1 tumor cells that had previously been transduced with the gene therapy vector encoding the accessory molecule ligand gene (murine CD40) as described above.

Each group of mice was allowed to generate an 35 immune response for 10 days. After 10 days each mouse

was challenged with 1.0×10^4 live, non-irradiated Line1 neoplastic cells. These mice were then monitored for the formation of tumors and then sacrificed when the tumors grew to 2.0 cm because of morbidity. The results 5 of this monitoring are shown in Figure 7. As can be seen by Figure 7, the mice immunized with the neoplastic cell expressing the accessory molecule ligands of the present invention on the cell surface remained free of tumor throughout the experiment. Mice immunized with 10 the neoplastic cells not having the accessory molecule ligand genes of the present invention succumbed to tumor 50 days after challenge with the neoplastic cells.

Figure 21 demonstrates downmodulation of human CD40L, but not murine CD40L, in lung tumor cell lines 15 that express CD40. Human cell lines HeLa (CD40-negative cervical carcinoma, Figure 21A), A427 (CD40-negative lung carcinoma, Figure 21B), NCI 460 (weakly CD40- positive lung large cell carcinoma, Figure 21C), and SK- Mes-1 (strongly CD40-positive lung squamous cell tumor, 20 Figure 21D) were infected with adenovirus encoding lac-Z (Ad-LacZ), murine CD40L (Ad-mCD40L), and human CD40L (Ad-hCD40L) at an MOI of 0 (Blank), 1, and 10. 48 hours after infection, murine CD40L and human CD40L surface expression was determined. The percentage of cells that 25 express ligand are plotted on the Y-axis. Human and mouse CD40L are expressed at equal levels in CD40- negative cell lines. However, only murine CD40L expression is stable on cell lines that express CD40. In contrast to mCD40L, human CD40L is downmodulated on 30 CD40-positive tumors.

The data graphed in Figure 22A show that CD40 binding induces expression of tumor surface markers. Treating CD40-expressing lung cancer cell lines with α CD40 mAb resulted in enhanced expression of the tumor 35 cell surface markers CD95 (Fas), CD54 (ICAM-1) and class

I major histocompatibility antigens (MHC I). NCI 460, a weakly CD40-positive lung large cell carcinoma, was incubated with a CD40-specific monoclonal antibody (thick line), or MOPC21, an isotype control mAb (thin line), on CD32-expressing mouse fibroblasts for 48 hours. Following the 48 hr incubation, the lung tumor cells were analyzed for CD95, CD54, and MHC-I expression by FACS.

Figure 22B again shows downmodulation of human CD40L by CD40-positive tumor cells. HeLa (CD40-negative), CLL (CD40-positive), and SK-MES-1 (CD40-positive) tumor cells were cocultured for 24 hours with CD3-activated normal donor T cells at a tumor cell:T cell ration of 2.5:1. Following coculture, CD2-expressing T cells were analyzed for CD40L surface expression by FACS. Thin lines represent T cells stained with FITC-labeled isotype control antibody (MOPC21) and thick lines represent activated T cells stained with FITC-labeled α CD40L antibody (α CD154 antibody). The CD40-positive tumor cell lines, SK-MES-1, and CLL, do not express CD40 ligand on their surfaces.

5. Expression of the Human and Mouse Accessory Molecule Ligand, Fas Ligand, in Human Blood Lymphocytes

a. Construction of a Genetic Construct and Gene Therapy Vector Containing the Human and Mouse Fas Ligand Gene

30

Either the human accessory molecule ligand gene (human Fas ligand) or the murine accessory molecule ligand gene (murine Fas ligand) was constructed utilizing the respective human and murine genes.

An altered accessory cell molecule, in which a putative MMP-cleavage site was removed, was made and designated ΔFasL-pcDNA3. The nucleotide sequence of ΔFasL-pcDNA3 is listed as SEQ ID NO: 40. Human Fas ligand

5 nucleotides 325 to 342, encoding six amino acids, are missing from ΔFasL. The design of ΔFasL was based on reasoning that Domain III contains sites most accessible to MMPs, and could thus be the target on the molecule for cleavage from the surface of the cell. Sequences of

10 the human Fas ligand gene have been determined and are listed as SEQ ID NOS: 13 and 30 (Genbank accession U11821). Sequences of mouse Fas ligand genes have been determined and are listed as SEQ ID NOS: 14 (C57BL/6, Genbank accession U10984) and 31 (Balb/c, Genbank accession U58995). The sequence of the rat Fas ligand gene has been determined and is listed as SEQ ID NO: 25 (Genbank accession U03470). Chimeric constructs are made, as described in Example 2 for CD40 ligand chimeric constructs, in which Domain III of human Fas ligand is

15 replaced with Domains of other proteins, particularly proteins of the TNF family. Chimeric constructs include, but are not limited to, human Fas ligand with Domain III replaced by Domain III of murine Fas ligand (chimeric sequence listed as SEQ ID NO: 37, sequence line-up shown in Figure 37), or replaced by Domain III of human CD70 (chimeric sequence listed as SEQ ID NO: 38, sequence line-up shown in Figure 38), or replaced with Domain I of human CD70 (chimeric sequence listed as SEQ ID NO: 39, sequence line-up shown in Figure 39).

20 Chimeric constructs in which multiple domains, for example, two copies of human CD70 Domain III, are inserted into human Fas ligand in place of Domain III, are also made using methods described in Example I.

25 Chimeric constructs in which synthetic sequences are

used to replace Domain III of human Fas ligand are also made.

5 i. Human Fas Ligand Cloning

The cDNA encoding human Fas-ligand was subcloned in the eukaryotic expression vector pcDNA3. Normal donor blood lymphocytes were activated for 4 hours with 1 ng/ml PMA plus 0.5 uM ionomycin. Total RNA was isolated 10 with the Qiagen Rneasy kit. cDNA was then synthesized from poly-A RNA with oligo-dT primers using the Gibco-BRL Superscript cDNA synthesis kit. The gene encoding human Fas-ligand was then PCR amplified with the Fas-ligand-specific primers (sense primer, SEQ ID NO: 32, 15 antisense primer, SEQ ID NO: 33). The Fas-ligand PCR product was then subcloned into pcDNA3 using standard molecular biology techniques. RT-PCR products, subcloned into pcDNA3, are designated hFasL-pcDNA3.

20 ii. Murine Fas Ligand Cloning

The murine Fas-ligand genes from Balb/c and C57/BL6 strains of mice were also amplified following activation of mouse splenocytes with PMA plus ionomycin as 25 described above, and amplified from poly-A synthesized cDNA as described above (sense primer, SEQ ID NO: 34, antisense primer, SEQ ID NO: 35). These genes were subcloned in the pTARGET expression vector (Promega, Madison, WI). RT-PCR products, subcloned into pcDNA3, 30 are designated mFasL-pcDNA3.

iii. Adenovirus Vector Construction

For construction of adenovirus vectors encoding 35 human Fas-ligand, murine Fas-ligand or ΔFas-ligand, the

cloned cDNA insert is subcloned into the plasmid pRc/RSV (Invitrogen, San Diego, CA) at the HindIII-XbaI site. A BglII-XbaI fragment with the RSV promoter-enhancer and the bovine growth hormone poly-A signal sequence was
5 subcloned into the BamHI-XbaI site of plasmid
MCS(SK)pXCX2. The plasmid MCS(SK)pXCX2 is a modification
of the plasmid pXCX2, in which the pBluescript polylinker
sequence was cloned into the E1 region. The resulting
plasmid then is co-transfected along with pJM17 into 293
10 cells using the calcium phosphate method. Isolated
plaques of adenovirus vectors are picked and expanded by
infecting 293 cells. High titer adenovirus preparations
are obtained, as described above which uses a cesium
chloride gradient for concentrating virus particles via a
15 step gradient, with the densities of 1.45g/cm³ and
1.20g/cm³, in which samples are centrifuged for 2 hours
in an SW41 rotor (Beckman, Brea, CA) at 25,000 rpm at 4°
C. The virus band is desalted using a Sephadex G-25 DNA
grade column (Pharmacia, Piscataway, NJ), and the
20 isolated virus is stored at -70° C in phosphate-buffered
saline with 10% glycerol. The titer of the virus is
determined by infecting permissive 293 cells at various
dilutions and counting the number of plaques. Titters
typically range from 10¹⁰ to 10¹² plaque forming units/ml.
25 The adenovirus constructs are designated Ad-hFasL, Ad-
mFasL and Ad-ΔFasL.

b. Introduction of the Murine and Human Fas Ligand
Genes into Human Cells

30

The constructs hFasL-pcDNA3, mFasL-pcDNA3 and ΔFasL-
pcDNA3 are transfected into 293 via electroporation. The
transfected cells are selected in medium containing G418.
35 Fas-ligand transfectants are screened for expression of
the transgene using anti-Fas-ligand antibody and flow

cytometry. The methods used are similar to those described for transfection of CD40L into CLL cells.

For FasL-adenovirus infection, 10⁶ freshly thawed and washed CLL cells or HeLa cells are suspended in 0.5 5 to 1 mL of culture medium for culture at 37°C in a 5% CO₂-in-air incubator. Adenovirus are added to the cells at varying multiplicity of infection (MOI), and the infected cells are cultured for 48 hours, unless otherwise stated, before being analyzed for transgene expression.

10

c. Expression of the Fas Ligand Genes in Human Cells

Mice with the lymphoproliferative or generalized 15 lymphoproliferative disorder are unable to delete activated self-reactive cells outside of the thymus. This is related to the fact that, in these mice, interactions between the Fas receptor and an accessory molecule ligand, Fas ligand, are defective. These 20 animals develop numerous disorders including lymphadenopathy, splenomegaly, nephritis, and systemic autoimmune pathology which resembles that seen in patients with systemic lupus erythematosus or rheumatoid arthritis (RA). It is conceivable that the normal 25 interactions between the Fas receptor and the accessory molecule ligand that are responsible for clearance of activated lymphocytes from joints may be impaired in RA patients.

RA synovial lymphocytes express the Fas receptor at 30 a higher proportion than that of matched RA blood lymphocytes to matched normal donor blood lymphocytes. On the other hand, RA synovial lymphocytes express little or no accessory molecule ligand. Since the RA synovial 35 lymphocytes are sensitive to Fas-induced apoptosis, it is feasible that local expression of Fas ligand in the RA

joint could serve to eliminate the synovial mononuclear cells that potentially mediate RA autoimmune pathology.

Figure 23 shows that Fas-ligand expression in lymphocytes is inhibited by exposure to RA synovial fluid. Normal donor blood T cells were activated for 5 hours with 1 ng/ml PMA plus 0.5 μ M ionomycin. Cells were incubated in the presence of rheumatoid arthritis blood plasma (circles), RA synovial fluid (diamonds), or neither (squares). In addition, cells were incubated with increasing concentrations of the MMP inhibitor BB94. Following activation, cells were analyzed for Fas-ligand surface expression by FACS. The percentage of cells expressing Fas ligand are plotted in Figure 23. This experiment demonstrates that there is a factor(s) present in RA synovial fluid and serum that prevents surface expression of Fas-ligand.

20 d. Function of Human, Murine and Chimeric Accessory Molecule Ligand, Fas Ligand

To determine the capacity of the Δ FasL constructs, the above-mentioned transfected cells are mixed with the Fas-ligand sensitive human T cell line, JURKAT. 25 Following 4 hours coculture, the nonadherent JURKAT cells are collected and evaluated for apoptosis. The fluorescent compound 3,3' dihexyloxacarbocyanine iodide (DiOC₆) is used to evaluate for apoptosis using a modification of a previously described protocol. For 30 this, the cells are washed once at room temperature in phosphate buffered saline (PBS, pH 7.2). Cells are placed into separate wells of a 96 well U-bottom plastic microtiter plate at 10^5 - 5×10^5 cells/well in 50 ml total volume. If indicated, saturating amounts of PE-conjugated antibodies are added followed by addition of 35

DiOC₆ and propidium iodide (PI). DiOC₆ and PI are used at 40 nM and 10 ng/ml final concentrations, respectively. The cells are then incubated 15 minutes in a 37°C, 5% CO₂ tissue culture incubator. The stained cells are then 5 washed twice in ice cold PBS and ultimately suspended in 200 ml SM and analyzed by FACS. Dead cells and debris with characteristic forward and light scatter profiles and PI staining are excluded from analysis.

The ability of cells expressing ΔFasL-pcDNA3 to 10 direct Fas-mediated apoptosis of cells expressing CD95 is compared with that of cells expressing FasL-pcDNA3. Relative stability of the protein products encoded by ΔFasL-pcDNA3 or FasL-pcDNA3 pre- and post- culture with RA synovial fluid, and with or without the 15 metalloproteinase inhibitors, are assessed via flow cytometry of cells expressing either ligand.

6. Treatment of Arthritis with Gene Therapy

Vectors Encoding an Accessory Molecule Ligand, Fas Ligand

20 The heterologous Fas-ligand constructs, made as described above, that show the highest stability of expression in combination with the greatest ability to mediate Fas-induced apoptosis, are used in gene therapy 25 for RA. Potential therapeutic constructs are tested in well-characterized mouse models of arthritis to assess efficacy and function *in vivo*.

a. Gene Therapy Treatment of Arthritis in Mice

i. Mouse Models for Arthritis

One mouse arthritis model is collagen-induced arthritis. It is known that injecting DBA/1 mice with 35 type II collagen in complete Freund's adjuvant (CFA)

induces an arthritis with synovitis and erosions that histologically resemble RA. For our studies, male DBA/1 mice are immunized with bovine type II collagen in complete Freund's adjuvant on day 0 and boosted 5 intraperitoneally (i.p.) on day 21. On day 28, animals are given an additional i.p. injection with lipopolysaccharide (LPS) and/or the same type collagen, or an injection of acetic acid alone. Swelling and/or redness of a fore or hind paw in animals immunized with 10 collagen typically is detected the third or fourth week following the second injection. The vertebrae are only rarely affected, and then only weeks after the initial peripheral joint swelling. Affected joints display 15 initial histologic changes of synovial edema, followed by synovial hyperplasia.

Another animal model, recently described by Kouskoff, V. et al., in Cell 87:811-822 (1997) was generated fortuitously, by crossing a T cell receptor (TCR) transgenic mouse line with the non-obese-diabetic 20 (NOD) strain to produce the KRN x NOD mouse model of RA. The offspring of such a mating universally develop a joint disease that is highly similar to that of patients with RA. Moreover, the disease in these animals has an early and reproducible time of onset and a highly 25 reproducible course. The arthritis apparently is induced by chance recognition of an NOD-derived major histocompatibility complex (MHC) class II molecule by the transgenic TCR, leading to breakdown in the general mechanisms of self-tolerance and systemic self- 30 reactivity.

ii. Relief of Arthritis Symptoms in Mice
Treated with a Gene Therapy Vector
Encoding an Accessory Molecule Ligand

5 We have adapted and modified a protocol originally described by Sawchuk and colleagues for micro-injecting adenovirus vectors into mouse joints. Using this procedure we can reproducibly inject a 5 μ l volume into the articular space of the mouse knee. In this
10 procedure, the mice are anesthetized with metofane. A small incision of approximately 2-3 mm is made with a #11 scalpel blade in the skin over the lateral aspect of the knee to visualize the patello-tibial ligament. We can inject up to 5 μ l of fluid using a micro-100 μ l-Hamilton
15 syringe and a 30-gauge needle. After the injection, the knee incision is closed with Nexabond (Veterinary Products Laboratory). Our adenovirus titers typically exceed 10^{10} plaque forming units (pfu) per ml, making it possible to deliver at least 5×10^8 pfu of virus in 5 ml
20 into the knee joints, as outlined above. Control animals are injected with control Ad-lacZ vector, a replication-defective adenovirus vector lacking a transgene, or with the buffer used to suspend the virus (10 mM Tris, 1 mM MgCl₂, 10% glycerol).

25 In another method, splenocytes will be harvested from mice that are syngeneic to the host animal intended for adoptive transfer of transduced cells. Cell proliferation will be induced with exogenous IL-12 (100 units/ml) for 48 h. Cells are counted and then re-plated
30 at densities of 5×10^5 or 1×10^6 cells per ml in a 12-well dish with 1 ml complete culture medium per well. Virus and ConA are added together at the time of re-plating in the presence of polybrene (8 μ g/ml). The medium is changed 24 hours after infection with complete
35 medium containing 100 units of recombinant IL-2 per ml.

Aliquots of the transduced cells are examined, for Fas-ligand expression, at 48 hours after infection via flow cytometry.

Animals will receive standardized numbers of cytokine-producing cells or control mock-transfected cells intraperitoneally. Concentrated cell suspensions are injected directly into the mouse synovium, as described in section 4A above. In parallel, aliquots of the transferred cell populations are maintained in tissue culture supplemented with exogenous IL-2.

Mice are monitored in a blinded fashion for signs of arthritis. The date of disease onset is recorded and clinical severity of each joint or group of joints (toes, tarsus, ankle, wrist, knee) are graded as follows: 0 (normal), 1 (erythema), 2 (swelling), 3 (deformity), 4 (necrosis). The scores are summed to yield the arthritic score. The severity of arthritis is expressed both as the mean score observed on a given day, and as the mean of the maximal arthritic score reached by each mouse during the clinical course of the disease. At the time of death, hind paws are dissected free and processed for histologic examination or for RT-PCR. The histologic severity of the arthritis is scored on a scale of 0-3 for synovial proliferation and inflammatory cell infiltration, where a score of 0 = normal and 3 = severe.

For mice receiving intra-synovial injection of control of test adenovirus vector, the level of arthritis observed between contralateral sites is compared. In addition, the overall joint score minus that of the injected joint for the entire animal is compared with that observed in the joint injected with the control or test adenovirus vector.

Local administration of Fas-ligand adenovirus expression vectors will result in clearance of activated cells, as assessed by measuring the relative levels of

CD80 mRNA by quantitative RT-PCR. This treatment also will lead to an enhanced level. Also, whether such level of apoptosis identified in affected mouse synovial tissue is assessed by the TUNEL assay ("Terminal 5 deoxynucleotidyl transferase (TdT)-mediated dUTP Nick End Labeling"). TUNEL is performed by immersing the sections in TdT buffer (30 mM Tris-HCl, pH 7.2, 140 nM sodium cacodylate, 1 mM cobalt chloride), and then adding TdT (GIBCO BRL, Grand Island, NY) and biotinylated dUTP 10 (Boehringer Mannheim, Indianapolis, IN). The reaction is terminated by immersing the sections in TB buffer (300 mM sodium chloride, 30 mM sodium citrate). Subsequently, the samples are treated with peroxidase-labeled 15 streptavidin and then visualized using the VECTASTAIN ABC kit (Vector Laboratories Inc., Burlingame, CA). For immunohistochemistry, the sections are blocked with 4% skim milk for 30 minutes at room temperature, then incubated with biotinylated mAbs specific for mouse CD3, B220, CD80, or CD95 (Fas). These antibodies are 20 available from Pharmingen (San Diego, CA).

b. Treatment of Rheumatoid Arthritis Patients with a Gene Therapy Vector Encoding an Accessory Molecule Ligand, Fas Ligand

25 Candidate Fas-ligand constructs identified as having potential therapeutic benefit are used in human protocols to treat RA. Human protocols encompass either *in vivo* or *ex vivo* methods to deliver the Fas-ligand constructs. 30 Furthermore, the Fas-ligand constructs are potentially delivered by either viral or non-viral methods. Outlines of therapeutic strategies are described below.

An *ex vivo* therapy is similar to a protocol described for intra-articular transplantation of 35 autologous synoviocytes retrovirally transduced to

synthesize interleukin-1 receptor antagonist (Evan,
Christopher et. al., Clinical Trial to Assess the Safety,
Feasibility, and Efficacy of Transferring a Potentially
Anti-Arthritic Cytokine Gene to Human Joints with
5 Rheumatoid arhritis, Human Gene Therapy, Vol. 7, 1261-
1280). In this procedure, after clinical diagnosis of
RA, the synovium is harvested during total joint
replacement. The synoviocytes re-isolated and expanded,
then transduced or transfected with heterologous Fas-
10 ligand into synoviocytes (via retrovirus, adenovirus,
naked DNA, etc.). The gene-modified synoviocytes are
then reinjected into the patient, who is monitored and
tested for amelioration of RA-associated symptoms, and
for expression and function of the Fas-ligand in modified
15 synoviocytes.

In another ex vivo protocol, an allogeneic immortalized cell line that stably expresses the heterologous Fas-ligand is administered to the RA patient. In this protocol, a stable immortalized cell line expressing Fas-ligand (introduced by transfection of the gene into the cell by nonviral methods, such as electroporation), or by viral transduction of the gene into the cell) is constructed. The modified cell line is injected into the patient, who is monitored and tested for amelioration of RA associated symptoms, and for expression and function of the hFas-ligand in modified synoviocytes.

An in vivo based therapy will be similar in concept to the amelioration of collagen-induced-arthrits using a murine Fas-ligand adenovirus gene therapy vector, described in Zhang, et al., J. Clin. Invest. 100:1951-1957 (1997). In our use of such an approach, delivery of the hFas-ligand construct or chimeric Δ fasL directly to the joints of RA patients is performed using either viral or non-viral methods. In this procedure, the Fas-ligand

construct (e.g. hFas-ligand adenovirus) is directly injected into the synovium. Patients are monitored and tested for amelioration of RA-associated symptoms as well as biological testing for expression and function of the 5 hFas-ligand in modified synoviocytes.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANTS: Kipps, Thomas J.
Sharma, Sanjai
Cantwell, Mark
- (ii) TITLE OF INVENTION: NOVEL EXPRESSION VECTORS
CONTAINING ACCESSORY
MOLECULE LIGAND GENES AND
THEIR USE FOR IMMUNOMODULA-
TION AND TREATMENT OF
MALIGNANCIES AND AUTOIMMUNE
DISEASE
- (iii) NUMBER OF SEQUENCES: 35
- (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Lyon & Lyon
(B) STREET: 633 West Fifth Street
Suite 4700
(C) CITY: Los Angeles
(D) STATE: California
(E) COUNTRY: U.S.A.
(F) ZIP: 90071-2066
- (v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5" Diskette,
1.44 Mb storage
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: IBM P.C. DOS 5.0
(D) SOFTWARE: FastSeq Version 2.0
- (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: To Be Assigned
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 60/132145
(B) FILING DATE: 12/9/96

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Guise, Jeffrey W.
(B) REGISTRATION NUMBER: 34,613
(C) REFERENCE/DOCKET NUMBER: 231/003

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (213) 489-1600
(B) TELEFAX: (213) 955-0440
(C) TELEX: 67-3510

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 786 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

ATGATCGAAA	CATAACAACCA	AACCTCTCCC	CGATCTGCGG	CCACTGGACT	GCCCCATCAGC	60
ATGAAAATTT	TTATGTATTT	ACTTACTGTT	TTTCTTATCA	CCCAGATGAT	TGGGTCAGCA	120
CTTTTGCTG	TGTATCTTCA	TAGAAGGTTG	GACAAGATAG	AAGATGAAAG	GAATCTTCAT	180
GAAGATTTG	TATTGATGAA	AACGATACAG	AGATGCAACA	CAGGAGAAAG	ATCCTTATCC	240
TTACTGAAC	GTGAGGAGAT	AAAAGCCAG	TTTGAAGGCT	TTGTGAAGGA	TATAATGTTA	300
ACAAAGAGG	AGACGAAGAA	AGAAAACAGC	TTTGAATGC	AAAAGGTGA	TCAGAACCT	360
CAAATTGCGG	CACATGTCAT	AAGTGAGGCC	AGCAGTAAAA	CAACATCTGT	GTTACAGTGG	420
GCTGAAAAAG	GATACTACAC	CATGAGCAAC	AACTTGGTAA	CCCTGGAAAA	TGGGAAACAG	480
CTGACCGTTA	AAAGACAAGG	ACTCTATTAT	ATCTATGCC	AAGTCACCTT	CTGTTCCAAT	540
CGGGAAGCTT	CGAGTCAGC	TCCATTATA	GCCAGCCTCT	GCCTAAAGTC	CCCCGGTAGA	600
TTCGAGAGAA	TCTTACTCG	AGCTGCAAAT	ACCCACAGTT	CCGCCAAACC	TTGCGGGCAA	660
CAATCCATTC	ACTTGGGAGG	AGTATTGAA	TTGCAACCAG	GTGCTTCGGT	GTTTGTCAAT	720
GTGACTGATC	CAAGCCAAGT	GAGCCATGGC	ACTGGCTTCA	CGTCCTTGG	CTTACTCAAA	780
CTCTGA						786

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 783 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

ATGATAGAAA CATAACGCCA ACCTTCCCCC AGATCCGTGG CAACTGGACT TCCAGCGAGC	60
ATGAAAGATTT TTATGTATTT ACTTACTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG	120
CTTTTGCTG TGTATCTTCAGAAGATTG GATAAGGTCG AAGAGGAAGT AAACCTTCAT	180
GAAGATTTG TATTCTAAAA AAAGCTAAAG AGATGCAACA AAGGAGAAGG ATCTTTATCC	240
TTGCTGAACGTGAGAGAT GAGAAGGCAA TTTGAAGACC TTGTCAGGAA TATAACGTAA	300
AACAAAGAAG AGAAAAAGA AAACAGCTT GAAATGCAAA GAGGTGATGA GGATCCTCAA	360
ATTGCAGCAC ACGTTGTAAG CGAAGCCAAC AGTAATGCAG CATCCGTTCT ACAGTGGGCC	420
AAGAAAGGAT ATTATACCAT GAAAAGCAAC TTGGTAATGC TTGAAAATGG GAAACAGCTG	480
ACGGTTAAAAA GAGAAGGACT CTATTATGTC TACACTCAAG TCACCTTCTG CTCTAACCGG	540
GAGCCTTCGA GTCAACGCCATTCACTCGTC GGCCTCTGGC TGAAGGCCAG CATTGGATCT	600
GAGAGAATCT TACTCAAGGC GGCAAATACC CACAGTTCT CCCAGCTTG CGAGCAGCAG	660
TCTGTTCACT TGGCGGGAGT GTTGAATTA CAAGCTGGTG CTTCTGTGTT TGTCAACGTG	720
ACTGAAGCAA GCCAAGTGAT CCACAGAGTT GGCTTCTCAT CTTTGGCTT ACTCAAACTC	780
TGA	783

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 783 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

ATGATCGAAA CATAACACCA AACCTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
ATGAAAATTT TTATGTATTT ACTTACTGTT TTTCTTATCA CCCAGATGAT TGGGTCAGCA	120
CTTTTGCTG TGTATCTTCAGAAGATTG GATAAGGTCG AAGAGGAAGT AAACCTTCAT	180
GAAGATTTG TATTCTAAAA AAAGCTAAAG AGATGCAACA AAGGAGAAGG ATCTTTATCC	240
TTGCTGAACGTGAGAGAT GAGAAGGCAA TTTGAAGACC TTGTCAGGAA TATAACGTAA	300
AACAAAGAAG AGAAAAAGA AAACAGCTT GAAATGCAAA GAGGTGATGA GGATCCTCAA	360
ATTGCAGCAC ACGTTGTAAG CGAAGCCAAC AGTAATGCAG CATCCGTTCT ACAGTGGGCC	420
AAGAAAGGAT ATTATACCAT GAAAAGCAAC TTGGTAATGC TTGAAAATGG GAAACAGCTG	480
ACGGTTAAAAA GAGAAGGACT CTATTATGTC TACACTCAAG TCACCTTCTG CTCTAACCGG	540
GAGCCTTCGA GTCAACGCCATTCACTCGTC GGCCTCTGGC TGAAGGCCAG CATTGGATCT	600
GAGAGAATCT TACTCAAGGC GGCAAATACC CACAGTTCT CCCAGCTTG CGAGCAGCAG	660

TCTGTTCACT TGGGCGGAGT GTTTGAATTA CAAGCTGGTG CTTCTGTGTT TGTCAACGTG	720
ACTGAAGCAA GCCAAGTGAT CCACAGAGTT GGCTTCTCAT CTTTTGGCTT ACTCAAACTC	780
TGA	783

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 786 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

ATGATCGAAA CATACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
ATGAAAATT TTATGTATTT ACTTACTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG	120
CTTTTGCTG TGTATCTTCA TAGAAGGTIG GACAAGATAG AAGATGAAAG GAATCTTCAT	180
GAAGATTTG TATTGATGAA AACGATACAG AGATGCAACA CAGGAGAAAG ATCCTTATCC	240
TTACTGAAC GTGAGGAGAT TAAAAGCCAG TTTGAAGGCT TTGTGAAGGA TATAATGTTA	300
AACAAAGAGG AGACGAAGAA AGAAAACAGC TTTGAAATGC AAAAAGGTGA TCAGAACCT	360
CAAATTGCGG CACATGTCAT AAGTGAGGCC AGCAGTAAAA CAACATCTGT GTTACAGTGG	420
GCTGAAAAG GATACTACAC CATGAGCAAC AACTTGGTAA CCCTGGAAAA TGGGAAACAG	480
CTGACCGTTA AAAGACAAGG ACTCTATTAT ATCTATGCC AAGTCACCTT CTGTTCCAAT	540
CGGGAAGCTT CGAGTCAAGC TCCATTATA GCCAGCTCT GCCTAAAGTC CCCCCGGTAGA	600
TTCGAGAGAA TCTTACTTCAG AGCTGAAAT ACCCACAGTT CCGCCAAACC TTGCGGGCAA	660
CAATCCATTC ACTTGGGAGG AGTATTGAA TTGCAACCAG GTGCTTCGGT GTTTGTCAAT	720
GTGACTGATC CAAGCCAAGT GAGCCATGGC ACTGGCTTCA CGTCCTTGG CTTACTCAAA	780
CTCTGA	786

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 783 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

ATGATCGAAA CATACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
ATGAAAATT TTATGTATTT ACTTACTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG	120
CTTTTGCTG TGTATCTTCA TAGAAGATTG GATAAGTCG AAGAGGAAGT AAACCTTCAT	180
GAAGATTTG TATTGATAAA AAAGCTAAAG AGATGCAACA AAGGAGAAGG ATCTTATCC	240

TTGCTGAAC	GTGAGGAGAT	GAGAAGGCAA	TTTGAAGACC	TTGTCAAGGA	TATAACGTTA	300
AACAAAGAAG	AGAAAAAAAGA	AAACAGCTT	GAAATGCAA	GAGGTGATGA	GGATCCTCAA	360
ATTGCAGCAC	ACGTTGTAAG	CGAAGCCAAC	AGTAATGCAG	CATCCGTTCT	ACAGTGGGCC	420
AAGAAAGGAT	ATTATACCAT	GAAAAGCAAC	TTGGTAATGC	TTGAAAATGG	GAAACAGCTG	480
ACGTTAAAAA	GAGAAGGACT	CTATTATGTC	TACACTCAAG	TCACCTTCTG	CTCTAACCGG	540
GAGCCTTCGA	GTCAACGCC	ATTCACTCGTC	GGCCTCTGGC	TGAAGCCCAG	CATTGGATCT	600
GAGAGAAATCT	TACTCAAGGC	GGCAAATACC	CACAGTTCT	CCCAGCTTGT	CGAGCAGCAG	660
TCTGTTCACT	TGGCGGAGT	GTGGAATTA	CAAGCTGGTG	CTTCTGTGTT	TGTCAACGTG	720
ACTGAAGCAA	GCCAAGTGAT	CCACAGAGTT	GGCTTCTCAT	CTTTTGGCTT	ACTCAAACTC	780
	TGA					783

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 786 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

ATGATAGAAA	CATACAGCCA	ACCTTCCCCC	AGATCCGTGG	CAACTGGACT	TCCAGCGAGC	60
ATGAAGATTT	TTATGTATTT	ACTTACTGTT	TTTCTTATCA	CCCAGATGAT	TGGGTCAAGCA	120
CTTTTTGCTG	TGTATCTTCA	TAGAAGGTTG	GACAAGATAG	AAGATGAAAG	GAATCTTCAT	180
GAAGATTTG	TATTCATGAA	AACGATACAG	AGATGCAACA	CAGGAGAAAG	ATCCTTATCC	240
TTACTGAACT	GTGAGGAGAT	AAAAGCCAG	TTTGAAGGCT	TTGTGAAGGA	TATAATGTTA	300
AACAAAGAGG	AGACGAAGAA	AGAAAACAGC	TTGAAATGC	AAAAGGTGA	TCAGAACCT	360
CAAATTGCGG	CACATGTCAT	AAGTGAGGCC	AGCAGTAAAAA	CAACATCTGT	GTTACAGTGG	420
GCTGAAAAG	GATACTACAC	CATGAGCAAC	AACTTGGTAA	CCCTGGAAAA	TGGGAAACAG	480
CTGACCGTTA	AAAGACAAGG	ACTCTATTAT	ATCTATGCC	AGTCACCTT	CTGTTCCAAT	540
CGGGAAAGCTT	CGAGTCAGC	TCCATTATA	GCCAGCCTCT	GCCTAAAGTC	CCCCGGTAGA	600
TTCGAGAGAA	TCTTACTCAG	AGCTGCAAAT	ACCCACAGTT	CCGCCAAACC	TTGCGGGCAA	660
CAATCCATTC	ACTTGGGAGG	AGTATTGAA	TTGCAACCAG	GTGCTTCGGT	TTTGTCAAT	720
GTGACTGATC	CAAGCCAAGT	GAGCCATGGC	ACTGGCTTCA	CGTCCTTGG	CTTACTCAA	780
	CTCTGA					786

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 786 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

ATGATAGAAA CATAACGCCA ACCTTCCCCC AGATCCGTGG CAACTGGACT TCCAGCGAGC	60
ATGAAGATT TTATGTATTT ACTTACTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG	120
CTTTTTGCTG TGTATCTTCAG TAGAAGGTTG GACAAGATAG AAGATGAAAG GAATCTTCAT	180
GAAGATTTG TATTCATGAA AACGATACAG AGATGCAACA CAGGAGAAAG ATCCTTATCC	240
TTACTGAAC GTGAGGAGAT TAAAAGCCAG TTTGAAGGCT TTGTGAAGGA TATAATGTTA	300
AACAAAGAGG AGACGAAAGAA AGAAAACAGC TTTGAAATGC AAAAGGTGA TCAGAACCT	360
CAAATTGCGG CACATGTCAT AAGTGAGGCC AGCAGTAAAA CAACATCTGT GTTACAGTGG	420
GCTGAAAAAG GATACTACAC CATGAGCAAC AACTTGGTAA CCCTGGAAA TGGGAAACAG	480
CTGACCGTTA AAAGACAAGG ACTCTATTAT ATCTATGCC AAGTCACCTT CTGTTCCAAT	540
CGGGAAGCTT CGAGTCAGC TCCATTATA GCCAGCCTCT GCCTAAAGTC CCCCAGTAGA	600
TTCGAGAGAA TCTTACTTCAG AGCTGAAAT ACCCACAGTT CCGCCAAACC TTGCGGGCAA	660
CAATCCATTC ACTTGGGAGG AGTATTGAA TTGCAACCAG GTGCTTCGGT GTTTGTCAAT	720
GTGACTGATC CAAGCCAAGT GAGCCATGGC ACTGGCTTCA CGTCCTTGG CTTACTCAAA	780
CTCTGA	786

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 864 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

AACTCTAACG CAGCATGATC GAAACATACA GTCAACCTTC TCCCCGCTCC GTGGCCACTG	60
GACCACCTGT CAGTATGAAA ATTTTTATGT ATTTACTTAC AGTTTTCTT ATCACCCAGA	120
TGATTGGTCA AGCGCTTTT GCTGTGTATC TTCACAGACG ATTGGACAAG ATAGAAGACG	180
AAAGGAATCT TCATGAAGAT TTTGTGTTCA TGAAAACGAT ACAGAGATGC AATAAAGGAG	240
AGGGGTCTT ATCCTTACTG AACTGTGAGG AAATTAGAAG CCGGTTGAA GACTTGGTCA	300
AGGATATAAT GCAAAACAAA GAAGTAAAGA AGAAAAGAAA AAACTTGAA ATGCACAAGG	360
GTGATCAGGA GCCTCAGATA GCGGCACATG TCATCAGTGA GGCCAGTAGT AAAACAAACCT	420
CTGTTCTCCA GTGGGCCCCC AAAGGATACT ACACCCCTAAG CAACAACTG GTAACCCCTG	480
AAAACGGGAA ACAGCTGGCC GTGAAAAGAC AAGGATTCTA TTACATCTAC ACCCAAGTCA	540
CCTTCTGTT CAATCGGGAA ACTTTGAGTC AAGCTCCATT TATAGCCAGC CTCTGCCTGA	600
AGTCCCCAAG TGGATCAGAG AGAATCTTAC TGAGAGCTGC AAACACCCAC AGTTCTTCCA	660
AACCATGCGG GCAGCAATCC ATTCACTTAG GAGGAGTCTT TGAATTGCAA TCGGGTGCTT	720
CGGTGTTGT CAATGTGACT GATCCAAGTC AAGTGAGCCA CGGGACGGGC TTCACATCAT	780
TTGGCTTACT CAAACTCTGA ACGGTGTAAAG CCAGCAGGCT GCGGCTGGGC TGATGCTGGT	840
GGTCTTCACA ATCCAGGAAA GCAG	864

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3634 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GAATTCCGGG TGATTTCACT CCCGGCTGTC CAGGCTTGTC CTGCTACCCC ACCCAGCCTT	60
TCCTGAGGCC TCAAGCCTGC CACCAAGCCC CCAGCTCCTT CTCCCCGCAG GACCAAACA	120
CAGGCCTCAG GACTAACAC AGCTTTCC CCAACCCGT TTTCTCTCCC TCAACGGACT	180
CAGCTTCTG AAGCCCTCC CAGTTCTAGT TCTATCTTT TCCTGCATCC TGTCTGGAAG	240
TTAGAAGGAA ACAGACCACA GACCTGGTCC CAAAAAGAAA TGGAGGCAAT AGGTTTTGAG	300
GGGCATGGGG ACGGGGTTCA GCCTCCAGGG TCCTACACAC AAATCAGTCA GTGGCCCAGA	360
AGACCCCCCT CGGAATCGGA GCAGGGAGGA TGGGGACTGT GAGGGGTATC CTTGATGCTT	420
GTGTGTCCCC AACTTCAA ATCCCCGCC CCGCGATGGA GAAGAAACCG AGACAGAAGG	480
TGCAGGGCCC ACTACCGCTT CCTCCAGATG AGCTCATGGG TTTCTCCACC AAGGAAGTTT	540
TCCGCTGGTT GAATGATTCT TTCCCCGCC TCCTCTCGCC CCAGGGACAT ATAAAGGCAG	600
TTGTTGGCAC ACCCAGCCAG CAGACGCTCC CTCAGCAAGG ACAGCAGAGG ACCAGCTAAG	660
AGGGAGAGAA GCAACTACAG ACCCCCCCTG AAAACAACCC TCAGACGCCA CATCCCCTGA	720
CAAGCTGCCA GGCAGGTTCT CTTCTCTCA CATACTGACC CACGGCTTCA CCCTCTCTCC	780
CCTGGAAAGG ACACCATGAG CACTGAAAGC ATGATCCGGG ACCTGGAGCT GGCGGAGGAG	840
GCGCTCCCCA AGAAGACAGG GGGGCCCCAG GGCTCCAGGC GGTGTTGTT CCTCAGCTC	900
TTCTCCTTCC TGATCGTGGC AGGCGCCACC ACGCTTTCT GCCTGCTGCA CTTTGGAGTG	960
ATCGGCCCCC AGAGGAAGA GGTGAGTGCC TGGCCAGCCT TCATCCACTC TCCCACCCAA	1020
GGGGAAATGA GAGACCAAG AGAGGGAGAG AGATGGGATG GGTGAAAGAT GTGCGCTGAT	1080
AGGGAGGGAT GAGAGAGAAA AAAACATGGA GAAAGACGGG GATGCAGAAA GAGATGTGGC	1140
AAGAGATGGG GAAGAGAGAG AGAGAAAGAT GGAGAGACAG GATGTCTGGC ACATGGAAGG	1200
TGCTCACTAA GTGTGTATGG AGTGAATGAA TGAATGAATG AATGAACAAG CAGATATATA	1260
AATAAGATAT GGAGACAGAT GTGGGGTGTG AGAAGAGAGA TGGGGGAAGA AACAAAGTGAT	1320
ATGAATAAAG ATGGTGAGAC AGAAAGAGCG GGAAATATGA CAGCTAAGGA GAGAGATGGG	1380
GGAGATAAGG AGAGAAGAAG ATAGGGTGTG TGGCACACAG AAGACACTCA GGAAAGAGAGC	1440
TGTTGAATGC TGGAAAGGTGA ATACACAGAT GAATGGAGAG AGAAAACCG ACACCTCAGG	1500
GCTAAGAGCG CAGGCCAGAC AGGCAGCCAG CTGTTCTCC TTTAAGGGTG ACTCCCTCGA	1560
TGTTAACCAT TCTCCTTCTC CCCAACAGTT CCCCAGGGAC CTCTCTCTAA TCAGCCCTCT	1620
GGCCCAGGCA GTCAGTAAGT GTCTCCAAAC CTCTTCTCTA ATTCTGGGTT TGGGTTTGGG	1680
GGTAGGGTTA GTACCGGTAT GGAAGCAGTG GGGGAAATT AAAGTTTGG TCTTGGGGGA	1740
GGATGGATGG AGGTGAAAGT AGGGGGGTAT TTTCTAGGAA GTTTAAGGGT CTCAGCTTT	1800
TCTTTCTCT CTCCTCTCA GGATCATCTT CTCGAACCCC GAGTGACAAG CCTGTAGCCC	1860
ATGTTGTAGG TAAGAGCTCT GAGGATGTGT CTTGGAACCTT GGAGGGCTAG GATTGGGGA	1920
TTGAAGCCCG GCTGATGGTA GGCAGAACTT GGAGACAAATG TGAGAAGGAC TCGCTGAGCT	1980
CAAGGGAAAGG GTGGAGGAAC AGCACAGGCC TTAGTGGGAT ACTCAGAACG TCATGCCAG	2040
GTGGGATGTG GGATGACAGA CAGAGAGGAC AGGAACCGGA TGTGGGGTGG GCAGAGCTCG	2100
AGGGCCAGGA TGTGGAGAGT GAACCGACAT GGCCACACTG ACTCTCCTCT CCCTCTCTCC	2160
CTCCCTCCAG CAAACCTCA AGCTGAGGGG CAGCTCCAGT GGCTGAACCG CGGGGCCAAT	2220
GCCCTCCTGG CCAATGGCGT GGAGCTGAGA GATAACCAGC TGGTGGTGCC ATCAGAGGGC	2280

CTGTACCTCA	TCTACTCCCA	GGTCCTCTTC	AAGGGCCAAG	GCTGCCCTC	CACCATGTG	2340
CTCCTCACCC	ACACCATCAG	CCGCATGCC	GTCTCCTACC	AGACCAAGGT	CAACCTCCTC	2400
TCTGCCATCA	AGAGCCCCTG	CCAGAGGGAG	ACCCCAGAGG	GGGCTGAGGC	CAAGCCCTGG	2460
TATGAGGCCA	TCTATCTGGG	AGGGTCTTC	CAGCTGGAGA	AGGGTGAACCG	ACTCAGCGCT	2520
GAGATCAATC	GGCCCCGACTA	TCTCGACTTT	GCCGAGTCTG	GGCAGGTCTA	CTTTGGGATC	2580
ATTGCCCTGT	GAGGAGGACG	AACATCCAAC	CTTCCCAAAC	GCCTCCCCTG	CCCCAATCCC	2640
TTTATTACCC	CCTCCTTCAG	ACACCCCTAA	CCTCTCTGG	CTCAAAAAGA	GAATTGGGGG	2700
CTTAGGGTCG	GAACCCAAGC	TTAGAACTTT	AAGCAACAAG	ACCACCACTT	CGAAACCTGG	2760
GATTCAAGGAA	TGTGTGCCCT	GCACAGTGA	GTGCTGGCAA	CCACTAAGAA	TTCAAACTGG	2820
GGCCTCCAGA	ACTCACTGGG	GCCTACAGCT	TTGATCCCTG	ACATCTGGAA	TCTGGAGACC	2880
AGGGAGCCTT	TGGTTCTGGC	CAGAATGCTG	CAGGACTTGA	GAAGACCTCA	CCTAGAAATT	2940
GACACAAGTG	GACCTTAGGC	CTTCCTCTCT	CCAGATGTTT	CCAGACTTCC	TTGAGACACG	3000
GAGCCCCAGCC	CTCCCCATGG	AGCCAGCTCC	CTCTATTAT	GTGATTACTT	GTGATTATT	3060
ATTATTTATT	TATTATTAT	TTATTTACAG	ATGAATGTAT	TTATTTGGGA	GACGGGGTA	3120
TCCTGGGGGA	CCCAATGTAG	GAGCTGCCTT	GGCTCAGACA	TGTTTCCGT	AAAAACGGAG	3180
CTGAACAATA	GGCTGTCCC	ATGTAGCCCC	CTGGCCTCTG	TGCCTCTTT	TGATTATGTT	3240
TTTAAAATA	TTTATCTGAT	TAAGTTGTCT	AAACAATGCT	GATTGGTGA	CCAACTGTCA	3300
CTCATTGCTG	AGCCTCTGCT	CCCCAGGGGA	GTTGTGTCTG	TAATCGCCCT	ACTATTCACT	3360
GGCGAGAAAT	AAAGTTTGCT	TAGAAAAGAA	ACATGGTCTC	CTTCTGGAA	TTAATTCTGC	3420
ATCTGCCTCT	TCTTGTGGGT	GGGAAGAACG	TCCCTAAGTC	CTCTCTCCAC	AGGCTTTAAG	3480
ATCCCTCGGA	CCCAGTCCC	TCTTAGACT	CCTAGGGCCC	TGGAGACCT	ACATAAACAA	3540
AGCCCAACAG	AATATCCCC	ATCCCCCAGG	AAACAAAGAGC	CTGAACCTAA	TTACCTCTCC	3600
CTCAGGGCAT	GGGAATTTC	AACTCTGGGA	ATTC			3634

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1997 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GAGACAGAGT	CTTGCTCTGT	CCCCCAGGCT	GGAATACAGT	GGTGCAGATCT	TGACTCACTG	60
CAGCCTCCGC	CTTCCCAGGTT	CAAATAATTC	TCCAGCCTCA	GCCTCCCGAG	TAGCTGGGAC	120
TGAGATGCG	CACCAGCACG	CCTGGCTAAAT	TTTTGTATTT	ATTATAGAGA	TGGGGTTTCA	180
CCATGTTGGC	CAGCTGGTCT	CAAACCTCCTG	ACCTCAAGTA	ATCCGCCAC	CTCAGACTCC	240
CAAAGTGCCA	GGATTACAGG	TGTGAGCCAC	TGCACCAGGC	CTGGAACAAAT	TTTAAAATAA	300
TGTATTGGCT	CTGCAAATGC	AGCTTCAGAA	CAAGTCCCTT	AGCTGTCCCC	ACCCCAACCT	360
AAGTCACCAC	CCTTAAGCCT	CACCCATGTG	GAATTCTGAA	ACTTCCTTTG	TAGAAAACCT	420
TGGAAGGTGT	CTGCCACATT	GATCCTGGAA	TGTGTGTTA	TTTGGGGTTA	TATAATCTG	480
TTCTGTGGAA	GCCACCTGAA	GTCAGGAAGA	GATGGAGGGC	ATCCTTCAGG	AGTGAGATGA	540
GACCTCATCA	TACTTGACTG	TCCAGCATCA	TCTCTGAGTA	AGGGGACCAA	AAAATTTATC	600
TTCCAAACTA	GGACACTTTC	AAGAGTGGAA	GGGGGATCCA	TTAATATT	CACCTGGACA	660

AGAGGCAAAAC	ACCAGAATGT	CCCCGATGAA	GGGGATATAT	AATGGACCTT	CTTGATGTGA	720
AACCTGCCAG	ATGGGCTGGA	AAGTC CGTAT	ACTGGGACAA	GTATGATTG	AGTTGTTGG	780
GACAAGGACA	GGGGTACAAG	AGAAGGAAAT	GGGCAAAGAG	AGAAGCCTGT	ACTCAGCCAA	840
GGGTGCAGAG	ATGTTATATA	TGATTGCTCT	TCAGGAACC	GGGCCTCCAG	CTCACACCCC	900
AGCTGCTCAA	CCACCTCCTC	TCTGAATTGA	CTGTCCTTC	TTTGGAACTC	TAGGCCTGAC	960
CCC ACTCCCT	GGCCCTCCC	GCCCACGATT	CCCCTGACCC	GA CTCCTTT	CCCAGAACTC	1020
AGTCGCTGA	ACCCCCAGCC	TGTGGTTCTC	TCCTAGGCCT	CAGCCTTTCC	TGCCTTGAC	1080
TGAAACAGCA	GTATCTCTA	AGCCCTGGGG	GCTTCCCCGG	GCCCAGCCC	CGACCTAGAA	1140
CCC GCCC CGCT	GCCTGCCACG	CTGCCACTGC	CGCTTCCTCT	ATAAAGGGAC	CTGAGCGTCC	1200
GGGCCCAGGG	GCTCCGACA	GCAGGTGAGG	CTCTCCTGCC	CCATCTCCTT	GGGCTGCCCG	1260
TGCTTCGTGC	TTTGGACTAC	CGCCCA CGAG	TGTCCCTGCC	TCTGCCTGGG	CCTCGGTCCC	1320
TCCTGCACCT	GCTGCCTGGA	TCCCCGGCCT	GCCTGGGCCT	GGGCTTGGTG	GGTTGGTTT	1380
TGGTTCCCTT	CTCTGTCTCT	GACTCTCCAT	CTGTCAGTCT	CATTGTCTCT	GTCACACATT	1440
CTCTGTTCT	GCCATGATTC	CTCTCTGTT	CCTTCCTGTC	TCTCTCTGTC	TCCCTCTGCT	1500
CACCTGGGG	TTTCTCTGAC	TGCATCTTGT	CCCCTCTCT	GTCGATCTCT	CTCTCGGGGG	1560
TCGGGGGGTG	CTCTCTCCC	GGGC GGAGG	TCTGTCCTCC	GGCGCGTGCC	CCGCCCGCCT	1620
CACTGTCTCT	CTCTCTCTCT	CTCTTTCTCT	GCAGGTTCTC	CCC ATGACAC	CACCTGAACG	1680
TCTCTCCTC	CCAAGGGTGT	GTGGCACCA	CCTACACCTC	CTCCTCTG	GGCTGCTGCT	1740
GGTCTGCTG	CCTGGGGCCC	AGGTGAGGA	GCAGGAGAAT	GGGGGCTGCT	GGGGTGGCTC	1800
AGC CAAACCT	TGAGCCTAG	AGCCCCCCTC	AACTCTGTT	TCCCCTAGGG	GCTCCCTGGT	1860
GTTGGCCTCA	CACCTTCAGC	TGCCCAGACT	GCCCGTCAGC	ACCCCAAGAT	GCATCTGCC	1920
CACAGCACCC	TCAAACCTGC	TGCTCACCTC	ATTGGTAAAC	ATCCACCTGA	CCTCCCAGAC	1980
ATGTCCCCAC	CAGCTCT					1997

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 10240 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

GAATTCCCCG	GATCAAAGTC	AGCATTAAAT	CCCAGTTAG	TTTTGAGGC	TAAGTTCAAG	60
TTTGAGTCTA	ATGTCATTTC	AGCCTTGT	GGAGGACTCA	GAGATTCAC	TAGTTCTCC	120
GCAGAGACCA	CTGTAGAAC	TGCATTTCCC	TGAGTTTG	GCACAAGACT	CCAGTCATCA	180
CCCCTCCCAC	ACAGGGAAAG	CCCCAAACCA	ACTGCTGCC	TCCTCAAGAA	AGAAACCGAA	240
TTTCACACAA	CCTCCGAAAC	TAAGATTGAA	ACCAAGATTG	GCCCATCTCA	AGGCGCGTCC	300
TCCAGCACAT	TGAGAATGTC	GCTGATGGAG	CCTCGGCCA	GCTCTCGAGC	TTCCCTCC	360
TCTGTCTCTC	ATGTCCTCTC	ATCACTCCT	CTCACCTCC	CGTTTTGTC	CTGCAATGCC	420
CCCTTCTTCC	TCTCTTCC	GGGTTTTCC	CTTTATTTCT	CACTGTACCA	TTTTATATT	480
TAATAAAGCC	GAGGTCTCCT	AGTCCATCAG	CTCCTACTGT	TGGAGAGGAG	GCAGAAAGAA	540
ACAGCAGGAC	GGCAAAGGA	CTCCAGAGAA	AGAGACTCAG	AGGAAAGGCA	AGAACAGGG	600
ACCAAGAGAG	AGGCCAACAG	TGACACAAGA	CACAGTGAGG	TTAAAAGAAA	TAAGATGAGG	660
CCAAGATAGA	GACCAAGCTA	TTTAAAAGAG	CCATCTGTGG	CTACCCCTCT	TCCGCCATCG	720
CATCTGGTCA	GCCACCAAGA	TTTGCTCTAG	AAACGTTCC	CCTCTCCATT	CTCCTGCTGC	780

TGCTGCTGCT	GCTGCTGCTG	CTGCTGCTGC	TGCTGCTGCT	GCTGCTGCTG	CTGCCTTAAT	840
ACGAATGCAG	GCTCTTGTCA	TCTCCTTGCT	GGGTTGTTGC	AAAATCCTCC	TAACTGGTCT	900
CCACACTTCT	CATTTCCCCT	CCAGCCCCCC	ATCTTCATA	CTTCCATTAA	TTTATTTTGG	960
CCATGCCCAT	GGCATGTGGC	AGTTCCAGGG	GCCAGGGATC	AAACCTGTGC	CAATGCAGTG	1020
ACCGTGTCA	ATCCCTAAC	CACTGCACAC	AAGGCAACGC	CCCTCGAGTC	ATTCTCATT	1080
TTTAAATATA	CCAATTGAG	GGGGTCCCTC	TTTCACTTAA	AAATTTGGC	AGCTCCCTAT	1140
CATGATGAGA	AGGAATTCCA	AACCATT	CTTGTGTGCA	AACCCCTTCAG	CATGTGTCC	1200
CAGCTTACTT	CCCAAGCCTC	ATCCCTGCTC	CTTCTACGTG	TACCCATGTG	TACATCTCCA	1260
CACACCATA	ACTCTTTTT	ACCTCCCAC	TTTGACAC	CTGTTCCCTC	TCTCTGCC	1320
TCACCATCTT	TTTTGCTTTG	ATACTTAATG	CCTCTCCCTC	AGGCCAGGTT	CAATGGCTT	1380
TCTGTGGGCT	GCTTTAAGCC	CACTGTATG	GAACATTATCA	CATTTTATT	TATTTGACTT	1440
TCTTTTAGG	GCCGCAACCA	GCATATGGAG	ATTCCCAGGC	TAGGGATCTA	ATCGGAGCTG	1500
TATCTGCCAG	CCTGCGCTGG	AGCCACAGCA	ACGTGGGATC	CGAGCCTGAG	GGGTTTGAT	1560
GTCCTGTGGC	ACAGAAAGTTA	CATTCAAGCT	GTGCATGAAC	TATTTCTCCT	GTTCTCCTCC	1620
CCCTGCTTGA	GGCCCTGAG	CTTGCTCCTC	CATGCCTG	TGCTCTGACC	TATGACTT	1680
TTTGTGTTGC	ATTCCATCTC	TTAGTTTC	TCTCTGTTCC	ACAAACATT	ACTGAGCATC	1740
TACATGAGG	ATTGAGGATA	CGGATGGGAA	AGACAGTCCC	CTGACCTCTG	GGACCTCAA	1800
GACCAATTGT	GGAAGACTGG	TTGGTTATCA	GATAATTACA	ATGAAGTGTG	GGAGTCCCTG	1860
TCATGGGTCA	GCAGGTAATG	AACCCAGTAA	ACGATCCATG	AGGATGCAGA	TTCAATCCCT	1920
GGCCTTGCTC	AGCGGGTTAA	GGATCCAGCG	TTCCCACAA	CTGTGGGTGTA	GGTGCAGAT	1980
GCGACTCAGA	TCTTGCTATTG	CTGTGGCTGT	GGTGTAGGCT	GGTGGCTACC	CCTAGCCTGG	2040
GAACCTCCAT	ATGCCTCAGG	TGCGGCCCTA	AAAGACAAAA	AAAAAAAAGA	GAGAAACTT	2100
TCTTTTCTT	AATGTGTAAC	CTACAAGCTA	AGTGAAA	GGCTCCTATT	CCATAAACGTT	2160
TGTATCATT	TTCATACTAG	CCAAATACTA	GAAACAGGGA	TTTCCCGTCG	TGGTGCAGCA	2220
GAAACAAATT	CGACTAGGAA	CCATGAGGTT	CGGGGTTCGA	TCCCTGGCCT	TGCTCAGTGG	2280
GTAAAGGATC	CGGCGTTGCC	GTGAGCTGTG	GTGTAGGTCG	CAGATGTGGC	TCGGATCTAG	2340
TGTTGCTGTG	GCTCTGGTGT	AGGCCGGCAG	CAACAGCTCT	GATTAGACTC	CTAGCCTGAG	2400
AACCTCCATA	AGCTGTGGCT	GCGGCCCTAT	AAAGACAAAA	AAAAAAA	GGCCAAATAC	2460
TAGAAACAAA	CCAAATGCC	ATCAACAGAA	GAATAGATAA	TTAATTGGG	GTATATGCAC	2520
ACAATAGCAT	CACACAATAA	CATGCACACA	ATAACATCAC	AATGAAATAA	AAATTACTAC	2580
TGACAGACAC	AACCATAATAG	ATGAATTCA	CAAACACAAAC	AGCGAGAATA	AAAGCCAAGC	2640
ACAGATGAGT	TGTCTGTGTG	GATTCAATT	TATGAAGTTC	AAGCGCAGGA	AGAACCTTAAT	2700
CTATAGTGCAC	AGAGGTCA	GAGCAGTTGG	TTGTCTTGG	CAGGTATGAA	CTGGGAGTGG	2760
GCATGAGAGA	ACTTCTGGA	GACCTAAAAA	TATATTGGAC	TGGATGGTGG	CAACATGGCT	2820
ACAAGAAGAT	GGAAAAGTTC	CTCAGGCTGT	CCACTTGGGA	GACGGGCTTC	TCACGGGACC	2880
TAAGTTCTGC	ATCAGCAGAG	GGGGAAATCC	TTAATGATT	GACAATTACA	AAGTGTATTG	2940
GCTTTACCGA	TGTATTCTCA	ACACAATCCC	TCTGCTGTCC	CCACCCACC	CTAGGTCA	3000
ACCCTTAAGC	TCCACCTGTG	TGGAATTCTG	AAGCCTCCCC	TGTAGAGAAC	TTTAGCAGTT	3060
GCCACGTTCT	TTTGATGCA	GAACGTGTTG	TCTAGAGTTA	GACACATCTG	ATCTGTGGGG	3120
CCCACCCAAG	GTTGGGACAT	GGTGGGGGGC	GGCCTCTGC	AGTGAGATGA	AACCTCATTG	3180
TAGGTGATT	CGTGGCCTCA	TCCCTGAGTC	AGATCTTCCA	AATGAGGACA	CTTGGAGAG	3240
CAAAAGGGGG	CTCCCTGAAG	ATTTCCTCCA	GGACAGCAGG	AAACAAACAG	GATGCCCAG	3300
GCAGGAGGGT	ATAGAAGGGA	ACTTGTGAT	ATGAAATCAG	CCAGATGACC	TGGAAAATAC	3360
ACAGACTGGG	ACAAGTGTGA	CTTGAGCCTC	TTGGGCCCAG	GACAGGGGTA	CAGAGGAGGA	3420
AACGTGCACA	GAGAGAAGCC	CGTAATCAGC	CAAGGCTGCA	GAGGTGTTAT	ACATAATCGC	3480
TCTTCACGCA	ACCGGGCAAG	CAGCCCACCG	CCCAGCTGCA	CTCCATCTCC	TCCTCTGAAC	3540
TCACCGTCCC	TTCTCTGGAA	CTCCTAAGCC	TGACCCCGCT	CCCTGGCCCT	CCCAGCCCAC	3600
GGTTCCCTG	ACCCCAC	CTTTCCCAGA	ACTCAGTCAT	CTGAGCCCCC	AGCCTGCGTT	3660
CTCTCCTAGG	CCTCAGCCTT	TCCTGCCTTC	GCAGTGAAACA	GCAGCATCTT	CTAAGCCCTG	3720

GGCTTCCCCA	GGCCCCAGCC	CCGGCCTAGA	ACCCGCCAG	CCGACCTGCC	CACGCTGCCA	3780
CTGCCGGCTT	CCTCTATAAA	GGGACCCAGG	GCGCCAGAA	AGGGGCCAC	AGGGGTCCCG	3840
CACAGCAGGT	GAGACTCTCC	CACCCCATCT	CCTAGGGCTG	TCCGGGTGCT	GGACTCCCCC	3900
CTCACTTCGG	TCCCTCCGCC	CGCTCCCTGG	CCTTCCTGCC	CCTCCTGCAT	CTTCACCCCG	3960
GCCTGGGCCT	TGGTGGGTTT	GGTTTTGGTT	TGTTCTCTCT	GATTCTTTAT	CTGTCAGGCT	4020
CTTCTAGCT	CTCACACACT	CTGATCCCTC	TCTGTTCCCT	TCCCCATCTCT	GTTTCTCTCT	4080
GGGTCTCCCC	CTGCTCACCT	CGGGATTTCC	CTGAGTGCCT	CTGGTCCCCCT	TCTCTGTCTG	4140
GCGCCCCGTC	TCTTGCTCTCT	CGGGGTGGCT	GTCTCCGAGG	GCAGGAGGCC	TTCTCCGCA	4200
GGTGCCCCGC	CCCGCTCACT	GTCTCTCTCC	CCCCACAGGT	TTTCCCCATG	ACACCACCTG	4260
GACGCCCTCA	CCTCCGGAGG	GTGTGCAGCA	CCCCCATCCT	CCTCCCTCCG	GGGCTGCTGC	4320
TGGCCCTGCC	GCCCAGGCC	CAGGTGAGGC	AGCAGGAGAG	CGGGCCGTGG	GGGCAGCCTT	4380
CGCCAACCTT	GGGCCTCAGA	GCCTCTCTGA	CGCTCTTCTC	CCCTAGGGGC	TCCCTGGCGT	4440
CGGCCCTCCCA	CCCTCAGCTG	CACAGCCTGC	CCATCAGCAC	CCCCCAAAGC	ACTTGGCCAG	4500
AGGCACCCCTC	AAACCTGCCG	CTCACCTCGT	TGGTAAACAT	CCACCTGGCC	TCCCAGACCT	4560
GTAGCCCCCA	GTCCTCCTCC	TATGCCCCCTG	CTTCAGGGAC	TGAAGCATCC	CTCCCCCCCCA	4620
TCTCCCCCCC	CCCCCTAAAT	GGAGGCATCC	CACTCCCGAC	TCCCTCCCAA	CCATCCCCCA	4680
GGAACTCAGT	CCAGCACCTG	CTTCCTCAGG	GATTGAGACC	TCCGACCCCCC	AGGTCTTGA	4740
CTCCCACCCCC	CTCTGGCTCT	TCCTAGGAGA	CCCCAGCACC	CCGGACTCAC	TGCGCTGGAG	4800
AGCGAACACG	GATCGTGCCT	TCCTCCGCCA	TGGCTCTTGT	CTGAGCAACA	ACTCCCTGCT	4860
GGTCCCCACC	AGTGGCCTCT	ACTTTGTCTA	CTCCCCAGGTC	GTCTTCTCCG	GGGAAGGCTG	4920
CTTCCCCAAG	GCCACCCCCA	CCCCCTCTCTA	CCTGGCCAC	GAGGTCCAGC	TCTTCTCCCTC	4980
CCAGTACCCCC	TTCCACGTGC	CGCTCCCTCAG	CGCTCAGAAG	TCCGTGTGCC	CGGGGCCACA	5040
GGGACCTTGG	GTGCGCTCTG	TGTACCAAGGG	GGCTGTGTTC	CTGCTCACCC	AGGGAGATCA	5100
GCTGTCCACA	CACACAGACG	GCACCCCCCA	CCTGCTCCTC	AGCCCCAGTA	GCGTCTTCTT	5160
TGGAGCCTTC	GCTCTATAGA	AGAATCCAGA	AAGAAAAAAA	TTGGTTTCAA	GGCCTTCTCC	5220
CCTTTTCACC	TCCCTTATGA	CCACTTCGGA	GGTCACCGCG	CCTCTCCTCT	GACAATTTC	5280
AACAGTCTCA	TCTTCCCCCA	CGCTCAGCAC	CTGGAGCTTC	TGTAGAAGGA	ATTCTAGGCA	5340
CCTCGGGGGA	ACTGGAACCA	CCCCGGATGC	TCTGCTGAGG	ATCTGAATGC	CCGCTCTGGAG	5400
CCCTTCCCCCT	GTCCTGCCCG	TCTAGGGGCC	CTCGTCCAGG	ACGTGGAAGG	GAAGCTGACC	5460
CATGAGGGAC	TTTGAACCGA	TGACCGGAGC	GGTGTGGGGG	GGTTATTAT	GAAGGGAAA	5520
ATAAATTAT	TTATTATATGG	AGGATGGAGA	GAAGGGAATC	ACAGAGGGAT	GTCAGAAGAG	5580
TGTGACACAT	GTGCCCAAGA	GATAAAGTGA	CAGAAGGCAT	GGGCTCCAGA	TGACCCGGCC	5640
AGAGAGGGCA	AAAGTGGCTCA	GGAAAGGGCT	GCTTGACTGG	AGGCTCATGA	GGAGACGGCT	5700
GACCCTCGAT	GAAACCCAAT	AAAGCTCTT	TCTCTGAAAT	GCTGTCTGCT	CGTATCTGTC	5760
ACTCGGGAGG	GGAGAATTCT	CCAGATGTCT	CTAAGGAGTG	GAGGGAGGAC	AGGAATCAGA	5820
GGGGACGGGA	GCTGTGGGTG	TGTGATGAGG	CCTAAGGGGC	TCAGGTGAGA	GATGGCGGCC	5880
TCAGGGTGAC	GGCAGCCAGA	CCCCTGCAGG	AGAACGAGAT	GGTTCCTCTG	AGAACAGAAA	5940
GGAAGAGATG	CAGGGCCAAG	GTCTTGAGAA	CCGAGGTCGG	GGGTCGCCCTG	GCAGATATGG	6000
CCACAGGTAG	AGGGACAGAG	GAATAGGGGT	GACAGGAGGC	TTCCCGGGAG	AAGGGAACAC	6060
ACTGAGGGGT	GTTCGGGATT	CTGAGGGAGG	AGCACGGGGA	CGCCCTGGGA	GACATGCCGT	6120
CCAGGGCCAT	GAGGAGTGGG	AGAGCCTCTG	AGGCTAGCGG	CTGGAGATAC	AGGGACATTT	6180
GAGGAGACAC	GGTCATGGCC	AGGAGCCGCG	AGGGCCTGGA	CAGTCTCTAG	GAATCTCGAA	6240
GAAGCAGGAA	TTCTTGAGG	ATACGTGGCC	ACACAAAGGG	AGGCTGAGGT	GTGGGGACTT	6300
CATGCAGAAG	TCAGGGCCTC	ACATTCCCTT	GGAAAGCCGAG	ACTGAAACCA	GCAGCAGAGT	6360
TTTGGTGAAT	TCCTGTCAGA	GTGAAAGGAG	AAGGCCCGCC	ATGGTGGGTT	TGTGAATTCC	6420
CAGCCTGGCT	TCCTCTCCCT	CTGGGGCTGT	CCCAGGCCTG	TTCCTGCCGT	CCTCCCCCAG	6480
CCCGTGTAGG	GCCTCCAGCT	GCCCTTCTCC	CAGCTCCTCT	TCCCTCCAGG	AGACGAAACA	6540
TGGGTCTCA	CACCCAGCGC	GGTGTGCTCT	AAGTTTCTC	TCCATTAAGA	ACTCAGCTT	6600
CTGAAGCTCC	TCCCATTCCCT	AGTTCTACCC	CTACCTGAGC	CCTGTTCGGA	AATCAGAGAG	6660

AAATAGAAGT	CATCCCCAA	AGAAAAGGAA	TTTGTCCCCC	AAAGAACAG	AACTGTCCC	6720
CCAAAGAAAT	GGAAACAATG	GGAAATGGGA	GGCAGGGGG	ACCTGGGTC	CAGCTCCAG	6780
GGTCCTACAC	ACAGAGCACT	AACTGGCCA	GCAAGCCAC	CTCAGGATCC	GGGCAGGGAG	6840
GGTAGGAAGT	ATCCCCTGATG	CCTGGGTGTC	CCCAACTTC	CAAACGCCG	CCCCGCTAT	6900
GGAGATGAAA	CTAAGACAGA	AGGTGCAGGG	CCCGCTACCG	CTTCCTCCAG	ATGAGCTCAT	6960
GGGTTTCTCC	ACCAAGGAAG	TTTCCGCTG	GTTGAAAGAG	AGCCTCTCCC	CGCCCTCTTC	7020
TCACCCAGAG	CGTATAAATG	CAGCTGTTG	CACACCCAGC	CAGCAGAAGC	TCCCAGAGTG	7080
AGGACACCAAG	GGGACCAGCC	AGGAGAGAGA	CAAGCCATCT	CCAGGACCCC	CTAGAAATAA	7140
CCTCTCAGAA	GACACACCCCC	CGAACAGGCA	GCCGGACGAC	TCTCTCCCTC	TCACACGCTG	7200
CCCCGGGGCG	CCACCATCTC	CCAGCTGGAC	CTGAGCCCT	CTGAAAAAGA	CACCATGAGC	7260
ACTGAGAGCA	TGATCCGAGA	CCTGGAGCTG	GC GGAGGAGG	CGCTCGCCAA	GAAGGCCGGG	7320
GGCCCCCAGG	GCTCCAGGAG	GTGCCTGTGC	CTCAGCCTCT	TCTCCTTCCT	CCTGGTCGCA	7380
GGAGGCCACCA	CGCTCTCTG	CCTACTGCAC	TTCGAGGTTA	TCGGCCCCCA	GAAGGAAGAG	7440
GTGAGCGCCT	GGCCAGCCTT	GGCTCATTCT	CCCACCCGGA	GAGAAATGGG	GAAGAAAGAG	7500
GGCCAGAGAC	GAGCTGGGGG	AAAGAAGTGT	GCTGATGGGG	AGTGTGGGG	GGAAATCATG	7560
GAGAAAGATG	GGGAGGCAGA	AGGAGACGTG	GAGAGAGATG	GGGGGAGAGA	GAGAAGGATG	7620
GAGAGAAATC	CGGTGGCCCG	GCCCTTGGAA	ATGCTCTCTA	AATATTGTT	GCACGAATGA	7680
GTGAGTAAGC	AGGGACACCG	ATATAAAGAG	AGATGAGTAG	ACAGACAAAG	GGTGTGGTAG	7740
AAAGATAGGG	AAAAAACAAAG	TGATCTGGAT	AAAGATAGTG	AGACAGGAAAG	AGGTAGAGGA	7800
GATAGGAAAG	AGAGATAAGG	AGAGAAGAAG	GAAGCGTGGG	TGTCTGGCAC	GTGGAAGGCA	7860
CTCAATGAAG	GAGTTGTTGA	ATGGATGGGT	GGATGAGAAA	ATGGATGAGT	GGAGAGAAAA	7920
AACTAGACAT	CAGGGCAGAG	AGTACAAGCT	AGAGAAGCAG	GTGGCTGTT	TCCCTTCAGA	7980
GGGGACTTAT	TCAAATCTAA	TTAATCCTTC	TTCTCTCCC	CAACAGTTTC	CAGCTGGCCC	8040
CTTGAGCATC	AACCCTCTGG	CCCAAGGACT	CACTAAGTAT	CTCTAAAACC	TGTCTCTCAG	8100
TTCTGAGCTT	GGACAGGGGT	GGGGTTAGTG	CTGGGGTGG	AGGAAGAAGG	GAAATTAGG	8160
GTCTGGTTT	GGCGGGGGGA	ATGCAGGTCA	AAGTAGTGAG	ATATTTCTG	GGAAGTCTGA	8220
GGGTCTCATC	TTTTCTTTC	CTCTTCCCTC	CTCAGGATCA	TCGTCTAAA	CCTCAGATAA	8280
GCCCCTCGCC	CACGTTGTAG	GTAAGAGTC	TGAGGATGTG	TCTGGGGAT	GAAGAAATAG	8340
GCAGGACAGA	GAGGGATAGG	ATTGGGGGGC	TGAAGCCAGG	CTGAGGGTAG	CCAGAGCTTG	8400
GAGATAGTAT	GAGGAGGACT	CGCTGAGCTC	CAGGGGAGGA	TGGGGGATAC	TCAGAACTTG	8460
AGGAGGATAAC	TCGGAACCTC	ATGGACAGAT	GGGATGTGGG	AAGACAGACC	GAGGGGACAG	8520
GAACCGGATG	TGGGGGGCGG	GCAGAACTCG	AGGGCCAGGA	TGTGGAGAGT	GGAACTGACA	8580
GGGTCACACT	GACTCACCCC	TCCCTCTTGT	TCTCCTCCCT	CCAGCCAATG	TCAAAGCCGA	8640
GGGACAGCTC	CAATGGCAGA	GTGGGTATGC	CAATGCCCTC	CTGGCCAACG	GCGTGAAGCT	8700
GAAAGACAAAC	CAGCTGGTGG	TGCCGACAGA	TGGGCTGTAC	CTCATCTACT	CCCAGGTCTC	8760
CTTCAGGGC	CAAGGCTGCC	CTTCCACCAA	CGTTTCTCTC	ACTCACACCA	TCAGCCGCAT	8820
CGCCGTCTCC	TACCAGACCA	AGGTCAACCT	CCTCTCTGCC	ATCAAGAGCC	CTTGCCAGAG	8880
GGAGACCCCC	GAGGGGGCCG	AGGCCAACGCC	CTGGTACGAA	CCCACCTTAC	TGGGAGGGGT	8940
CTTCCAGCTG	GAGAAGGATG	ATCGACTCAG	TGCCGAGATC	AACCTGCCCG	ACTATCTGGA	9000
CTTTGCTGAA	TCTGGCAGG	TCTATTTGG	GATCATTGCC	CTGTGAGGGG	GCAGGACATC	9060
CGTTCCCTCC	CCTGTCATC	CCTTTATTAT	TTTACTCCTT	CAGACCCCT	CACGTCCCTC	9120
TGGTTTAGAA	AGAGAATGAG	GGGCTGGGG	CTGGGCTCCA	AGCTAAAAC	TTTAAACAAC	9180
AACAGCAACA	CTTAGAAATC	AGGGATTCA	GGATGTTG	CCTGGACAAC	CAGGCAC	9240
CCACCAACAA	GAATTGGAAC	TGGGGCTTCC	AGACTCGCTG	GGGTCTTGG	GTTGGATTC	9300
CTGGATGCAA	CCTGGGACAT	CTGGAATGTG	GCTGCCAGGG	AAGCTTGGGT	TCCAATCGGA	9360
ATACTTCAGA	ACATTCCCTG	AGAAGATTTC	ACCTCAATCT	TGATGACTTT	TTAGGCTTCC	9420
CTTTCTTCCA	ATTTTCCAGA	CTTCCCTGGG	ATGGGGAGCC	CAGCCCCAAA	CCCCACAGGC	9480
CAGCTCCCTC	TTATTATAT	TTGCACTTGG	CATTATTATT	TATTTATTAA	TTTATTATTT	9540
ATTTACTAGT	GAATGTATTT	ATTCAAGGAGG	GCGAGGTGTC	CTGGGAGACC	CAGCATAAGG	9600

GCTGCCTGG	TTCAGATGTG	TTTCTGTGA	AAACGGAGCT	GAACGTAGG	TTGCTCCCAC	9660
CTGGCCTCCT	AGCCTCTGTG	CCTCCTTTG	CTTATGTTT	AAAAAACAAA	TATTATCTG	9720
ATCGAGTTGT	CTAAATAATG	CTGATTTGGT	GACTAACCC	TCGCTACATC	GCTAACCTC	9780
TGCTCCCCAG	GGGAGTTGTG	TCTGTAACCG	CCCTACTGGT	CAGTGGCGAG	AAATAAAAGC	9840
GTGCTTAGAA	AAGAAATCTG	GCCTCTTCT	GCGACTGAAT	TCTGCATCTC	CTTGGGGGGG	9900
TGAGGCTGCT	CCCCAAAATT	CTTCTCCAC	CGGGCTTAGG	ATTCCCTGGG	CTTCACTCCT	9960
GAGCTGGAC	TGCCTGGCTC	AGGAGCCTCT	GCAAGAAACA	AAGCCCAGCC	AAACAGGTCC	10020
CTCCCCTAAG	AAAGGAACCT	GAAGGTAATT	ACCTCTCCCT	CAGGGTGTGG	GAATTCCAA	10080
GTCTGGGAAT	TCCTATCCAG	CTGGGGAAAGT	CTGCAGTGCA	GGTGAGACTT	CCGGCTGAAA	10140
GAGCCAGGGA	GCGGCCAGAT	GTCAGGTAC	CTGAACCAGA	GCCAAGGGAC	TTCCAGACAG	10200
TGAGGCAACT	GGGCTCCAAA	TAACCTGATC	CGGGGAATTC			10240

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1644 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

CCTCAGCGAG	GACAGCAAGG	GACTAGCCAG	GAGGGAGAAC	AGAAACTCCA	GAACATCCTG	60
GAAATAGCTC	CCAGAAAAGC	AAGCAGCCAA	CCAGGCAGGT	TCTGTCCCTT	TCACTCACTG	120
GCCAAGGCG	CCACATCTCC	CTCCAGAAAA	GACACCATGA	GCACAGAAAG	CATGATCCGC	180
GACGTGGAAC	TGGCAGAAGA	GGCACTCCCC	CAAAGATGG	GGGGCTTCCA	GAACCTCAGG	240
CGGTGCCTAT	GTCTCAGCCT	CTTCTCATTC	CTGCTGTGG	CAGGGGCCAC	CACGCTCTTC	300
TGTCTACTGA	ACTTCGGGT	GATCGGTCCC	CAAAGGGATG	AGAAGTTCCC	AAATGGCCTC	360
CCTCTCATCA	GTTCTATGGC	CCAGACCCTC	ACACTCAGAT	CATCTTCTCA	AAATTCGAGT	420
GACAAGCCTG	TAGCCCACGT	CGTAGCAAAC	CACCAAGTGG	AGGAGCAGCT	GGAGTGGCTG	480
AGCCAGCGCG	CCAACGCCCT	CCTGGCCAAC	GGCATGGATC	TCAAAGACAA	CCAACACTAGTG	540
GTGCCAGCGG	ATGGGTTGTA	CCTTGTCTAC	TCCCAGGTTC	TCTTCAAGGG	ACAAGGCTGC	600
CCCGACTACG	TGCTCCTCAC	CCACACCGTC	AGCCGATTG	CTATCTCATA	CCAGGAGAAA	660
GTCAACCTCC	TCTCTGCCGT	CAAGAGCCCC	TGCCCCAAGG	ACACCCCTGA	GGGGGCTGAG	720
CTCAAACCCCT	GGTATGAGCC	CATATACTG	GGAGGAGTCT	TCCAGCTGGA	GAAGGGGGAC	780
CAACTCAGCG	CTGAGGTCAA	TCTGCCAAG	TACTTAGACT	TTGGGGAGTC	CGGGCAGGTC	840
TACTTTGGAG	TCATTGCTCT	GTGAAGGGAA	TGGGTGTTCA	TCCATTCTCT	ACCCAGCCCC	900
CACTCTGACC	CCTTTACTCT	GACCCCTTTA	TTGTCTACTC	CTCAGAGGCC	CCAGTCTGTG	960
TCCCTCTAAC	TTAGAAAGGG	GATTATGGCT	CAGAGTCAA	CTCTGTGCTC	AGAGCTTTCA	1020
ACAACACTC	AGAAACACAA	GATGCTGGGA	CAGTGACCTG	GAACGTGGC	CTCTCATGCA	1080
CCACCATCAA	GGACTCAAAT	GGGCTTCCG	AATTCACTGG	AGCCTCGAAT	GTCCATTCCCT	1140
GAGTTCTGCA	AAGGGAGAGT	GGTCAGGTTG	CCTCTGTCTC	AGAATGAGGC	TGGATAAGAT	1200
CTCAGGCCTT	CCTACCTTCA	GACCTTCCA	GAACCTTCCC	TGAGGTGCAA	TGCACAGCCT	1260
TCCTCACAGA	GCCAGCCCCC	CTCTATTAT	ATTTGCACTT	ATTATTATT	ATTATTATT	1320
TATTTATTAA	TTTGCTTATG	AATGTATTAA	TTTGAAGGC	CGGGGTGTCC	TGGAGGACCC	1380
AGTGTGGGAA	GCTGTCTTCA	GACAGACATG	TTTCTGTGA	AAACGGAGCT	GAGCTGTCCC	1440

CACCTGGCCT	CTCTACCTTG	TTGCCTCCTC	TTTGCTTAT	GTTTAAAACA	AAATATTTAT	1500
CTAACCCAAT	TGTCTTAATA	ACGCTGATT	GGTGACCAGG	CTGTCGCTAC	ATCACTGAAC	1560
CTCTGCTCCC	CACGGGAGCC	GTGACTGTAA	TTGCCCTACA	GTCAATTGAG	AGAAATAAAG	1620
ATCGCTTAAA	ATAAAAAAACC	CCCC				1644

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1890 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

AAACAGAGAG	AGATAGAGAA	AGAGAAAGAC	AGAGGTGTTT	CCCTTAGCTA	TGGAAACTCT	60
ATAAGAGAGA	TCCAGCTTGC	CTCCTTGTG	GCAGTCAGCA	ACAGGGTCCC	GTCCTTGACA	120
CCTCAGCCTC	TACAGGACTG	AGAAGAAGTA	AAACCGTTG	CTGGGGCTGG	CCTGACTCAC	180
CAGCTGCCAT	GCAGCAGCCC	TTCAATTACC	CATATCCCCA	GATCTACTGG	GTGGACAGCA	240
GTGCCAGCTC	TCCCTGGGCC	CCTCCAGGCA	CAGTTCTTCC	CTGTCCAACC	TCTGTGCCCA	300
GAAGGCCTGG	TCAAAGGAGG	CCACCACAC	CACCGCCACC	GCCACCACTA	CCACCTCCGC	360
CGCCGCCGCC	ACCACTGCCT	CCACTACCAC	TGCCACCCCT	GAAGAAGAGA	GGGAACCACA	420
GCACAGGCCT	GTGTCTCCTT	GTGATGTTT	TCATGGTTCT	GGTTGCCTTG	GTAGGATTGG	480
GCCTGGGGAT	GTTCAGCTC	TTCCACCTAC	AGAAGGAGCT	GGCAGAACTC	CGAGAGTCTA	540
CCAGCCAGAT	GCACACAGCA	TCATCTTGG	AGAAGCAAAT	AGGCCACCCC	AGTCCACCCC	600
CTGAAAAAAA	GGAGCTGAGG	AAAGTGGCCC	ATTTAACAGG	CAAGTCCAAC	TCAAGGTCCA	660
TGCCTCTGGA	ATGGGAAGAC	ACCTATGGAA	TTGTCTGCT	TTCTGGAGTG	AAGTATAAGA	720
AGGGTGGCCT	TGTGATCAAT	GAAACTGGGC	TGTACTTTGT	ATATTCCAAA	GTATACTTCC	780
GGGGTCAATC	TTGCAACAAAC	CTGCCCTGCA	GCCACAAGGT	CTACATGAGG	AACTCTAAGT	840
ATCCCCAGGA	TCTGGTGATG	ATGGAGGGGA	AGATGATGAG	CTACTGCACT	ACTGGGCAGA	900
TGTGGGCCCG	CAGCAGCTAC	CTGGGGGCAG	TGTTCAATCT	TACCACTGCT	GATCATTTAT	960
ATGTCAACGT	ATCTGAGCTC	TCTCTGGTCA	ATTTTGAGGA	ATCTCAGACG	TTTTCGGCT	1020
TATATAAGCT	CTAAGAGAAG	CACTTTGGGA	TTCTTCCAT	TATGATTCTT	TGTTACAGGC	1080
ACCGAGAATG	TTGTATTTCAG	TGAGGGTCTT	CTTACATGCA	TTTGAGGTCA	AGTAAGAAGA	1140
CATGAACCAA	GTGGACCTTG	AGACCACAGG	GTTCAAAATG	TCTGTAGCTC	CTCAACTCAC	1200
CTAATGTTA	TGAGCCAGAC	AAATGGAGGA	ATATGACGGA	AGAACATAGA	ACTCTGGCT	1260
GCCATGTGAA	GAGGGAGAAG	CATGAAAAAG	CAGCTACCCA	GGTGTCTAC	ACTCATCTTA	1320
GTGCCTGAGA	GTATTAGGC	AGATTGAAAA	GGACACCTTT	TAACTCACCT	CTCAAGGTGG	1380
GCCTTGCTAC	CTCAAGGGGG	ACTGTCTTC	AGATAACATGG	TTGTGACCTG	AGGATTAAAG	1440
GGATGGAAAA	GGAAGACTAG	AGGCTTGAT	AATAAGCTAA	AGAGGCTGAA	AGAGGCCAAT	1500
GCCCCACTGG	CAGCATCTTC	ACTTCTAAAT	GCATATCCTG	AGCCATCGGT	GAAACTAACAA	1560
GATAAGCAAG	AGAGATGTTT	TGGGGACTCA	TTTCATTCCCT	AACACAGCAT	GTGTATTTC	1620
AGTGCCAATT	GTAGGGGTGT	GTGTGTGTGT	GTGTGTGTGT	GTGTATGACT	AAAGAGAGAA	1680
TGTAGATATT	GTGAAGTACA	TATTAGGAAA	ATATGGGTTG	CATTTGGTCA	AGATTTGAA	1740
TGCTTCCTGA	CAATCAACTC	TAATAGTGCT	AAAAAATCAT	TGATTGTCAG	CTACTAATGA	1800
TGTTTCCTA	TAATATAATA	ATATTTATG	TAGATGTGCA	TTTTGTGAA	ATGAAAACAT	1860
GTAATAAAAA	GTATATGTTA	GGATACAAAT				1890

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1541 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GGGTGTCTCA	CAGAGAACGA	AAGAGAACAG	AACAGGAGAA	ATGGTGTTC	CCTTGACTGC	60
GGAAAACTTA	TAAAGAAAAC	TTAGCTTCTC	TGGAGCAGTC	AGCGTCAGAG	TTCTGTCC	120
GACACCTGAG	TCTCCTCCAC	AAGGCTGTGA	GAAGGAAACC	CTTCCTGGG	GCTGGGTGCC	180
ATGCAGCAGC	CCATGAATT	CCCATGTCCC	CAGATCTCT	GGGTAGACAG	CAGTGCCACT	240
TCATCTTGGG	CTCCTCCAGG	GTCAGTTTT	CCCTGTCCAT	CTTGTGGGCC	TAGAGGGCCG	300
GACCAAAGGA	GACCGCCACC	TCCACCACCA	CCTGTGTAC	CACTACCACC	GCCATCACAA	360
CCACTCCCAC	TGCCGCCACT	GACCCCTCTA	AAGAAGAACG	ACCACAACAC	AAATCTGTGG	420
CTACCGGTGG	TATTTTCAT	GGTTCTGGTG	GCTCTGGTTG	GAATGGGATT	AGGAATGTAT	480
CAGCTCTTCC	ACCTGCAGAA	GGAACTGGCA	GAACTCCGTG	AGTTCACCAA	CCAAAGCCTT	540
AAAGTATCAT	CTTTGAAAAA	GCAAATAGCC	AACCCAGTA	CACCCCTCTGA	AAAAAAAGAG	600
CCGAGGAGTG	TGGCCCATT	AACAGGGAAC	CCCCACTCAA	GGTCCATCCC	TCTGGAATGG	660
GAAGACACAT	ATGGAACCGC	TCTGATCTCT	GGAGTGAAGT	ATAAGAAAGG	TGGCCTTGTG	720
ATCAAACGAAA	CTGGGTTGTA	CTTCGTGTAT	TCCAAAGTAT	ACTTCCGGGG	TCAGTCTTGC	780
AACAACCAGC	CCCTAAACCA	CAAGGTCTAT	ATGAGGAAC	CTAAGTATCC	TGAGGATCTG	840
GTGCTAATGG	AGGAGAACAG	GTTGAAC	TGCAC	TACTG	GCCAGATATG	900
AGCTACCTGG	GGGCAGTATT	CAATCTTACC	AGTGCTGACC	ATTTATATGT	CAACATATCT	960
CAACTCTCTC	TGATCAATT	TGAGGAATCT	AAGACCTTT	TCGGCTTGTA	TAAGCTTAA	1020
AAGAAAAAGC	ATTTTAAAT	GATCTACTAT	TCTTATCAT	GGGCACCAGG	AATATTGTCT	1080
TGAATGAGAG	TCTTCTTAAG	ACCTATTGAG	ATTAATTAAG	ACTACATGAG	CCACAAAGAC	1140
CTCATGACCC	CAAGGTCCAA	CAGGTCA	ATCCTTCATT	TTCTCGAGGT	CCATGGAGTG	1200
GTCCTTAATG	CCTGCATCAT	GAGCCAGATG	GAAGGAGGTC	TGTGACTGAG	GGACATAAAG	1260
CTTTGGGCTG	CTGTGTAGCA	ATGCAGAGGC	ACAGAGAACG	AACTGTCTGA	TGTTAAATGG	1320
CCAAGAGAAAT	TTAACCA	GAAGAACACA	CCTTACACT	CACTTCCAGG	GTGGGTCTAC	1380
TTACTACCTC	ACAGAGGCCG	TTTTGAGAC	ATAGTTGTGG	TATGAATATA	CAAGGGTGAG	1440
AAAGGAGGCT	CATTTGACTG	ATAAGCTAGA	GA	CTGAAAAA	AAGACAGTGT	1500
CCATTTTAC	TGTTACCTGA	TGTTTCTGA	GCCGACCTTT	G		1541

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 888 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GGCTGGTCCC	CTGACAGGTT	GAAGCAAGTA	GACGCCAGG	AGCCCCGGGA	GGGGCTGCA	60
GTTCCCTTCC	TTCCTTCTCG	GCAGCGCTCC	GCGCCCCAT	CGCCCTCCT	GCGCTAGCGG	120
AGGTGATCGC	CGCGGGCATG	CCGGAGGAGG	GTTCGGGCTG	CTCGGTGCGG	CGCAGGCCCT	180
ATGGGTGCGT	CCTGCGGGCT	GCTTGCTCC	CATTGGTCGC	GGGCTGGTG	ATCTGCCTCG	240
TGGTGTGCAT	CCAGCGCTTC	GCACAGGCTC	AGCAGCAGCT	GCCGCTCGAG	TCACTTGGGT	300
GGGACGTAGC	TGAGCTGCAG	CTGAATCACA	CAGGACCTCA	GCAGGACCCC	AGGCTATACT	360
GGCAGGGGGG	CCCAGCACTG	GGCCGCTCCT	TCCTGCATGG	ACCAGAGCTG	GACAAGGGC	420
AGCTACGTAT	CCATCGTGAT	GGCATCTACA	TGGTACACAT	CCAGGTGACG	CTGGCCATCT	480
GCTCCTCCAC	GACGGCCTCC	AGGCACCACC	CCACCAACCT	GGCCGTGGGA	ATCTGCTCTC	540
CCGCCTCCCG	TAGCATCAGC	CTGCTGCGTC	TCAGCCTCCA	CCAAGGTTGT	ACCATTGCCT	600
CCCAGCGCCT	GACGCCCTG	GGCCGAGGGG	ACACACTCTG	CACCAACCTC	ACTGGGACAC	660
TTTGCCTTC	CCGAAACACT	GATGAGACCT	TCTTTGGAGT	GCAGTGGGTG	CGCCCTGAC	720
CACTGCTGCT	GATTAGGGTT	TTTTAAATT	TATTTTATT	TATTTAAGTT	CAAGAGAAAA	780
AGTGTACACA	CAGGGGCCAC	CCGGGGTTGG	GGTGGGAGTG	TGGTGGGGGG	TAGTGGTGGC	840
AGGACAAGAG	AAGGCATTGA	GCTTTTCTT	TCATTTCCCT	ATTAAAAAA		888

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1906 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

CCAAGTCACA	TGATTCAAGGA	TTCAGGGGGA	GAATCCTTCT	TGGAACAGAG	ATGGGCCAG	60
AACTGAATCA	GATGAAGAGA	GATAAGGTGT	GATGTGGGGA	AGACTATATA	AAGAATGGAC	120
CCAGGGCTGC	AGCAAGCACT	CAACGGAATG	GCCCCCTCCTG	GAGACACAGC	CATGCATGTG	180
CCGGCGGGCT	CCGTGCCAG	CCACCTGGGG	ACCACGAGCC	GCAGCTATTT	CTATTGACC	240
ACAGCCACTC	TGGCTCTGTG	CCTTGTCTTC	ACGGTGGCCA	CTATTATGGT	TGGTGGTCGTT	300
CAGAGGACGG	ACTCCATTCC	CAACTCACCT	GACAACGTCC	CCCTCAAAGG	AGGAAATTGC	360
TCAGAAAGACC	TCTTATGTAT	CCTGAAAAGA	GCTCCATTCA	AGAAGTCATG	GGCCTACCTC	420
CAAGTGGCAA	AGCATCTAAA	AAAACACCAAG	TTGTCTTGGA	ACAAAGATGG	CATTCTCCAT	480
GGAGTCAGAT	ATCAGGATGG	GAATCTGGT	ATCCAATTCC	CTGGTTTGTA	CTTCATCATT	540
TGCCAACTGC	AGTTTCTTGT	ACAATGCCA	AATAATTCTG	TCGATCTGAA	GTTGGAGCTT	600
CTCATCAACA	AGCATATCAA	AAAACAGGCC	CTGGTGACAG	TGTGTGAGTC	TGGAATGCAA	660
ACGAAACACG	TATACCAGAA	TCTCTCTCAA	TTCTTGCTGG	ATTACCTGCA	GGTCAACACC	720
ACCATATCAG	TCAATGTGGA	TACATTCCAG	TACATAGATA	CAAGCACCTT	TCCTCTTGAG	780
AATGTGTTGT	CCATCTTCTT	ATACAGTAAT	TCAGACTGAA	CAGTTCTCT	TGGCCTTCAG	840
GAAGAAAGCG	CCTCTCTACC	ATACAGTATT	TCATCCCTCC	AAACACTTGG	GCAAAAGAA	900
AACTTCTAGAC	CAAGACAAAC	TACACAGGGT	ATTAAATAGT	ATACTTCTCC	TTCTGTCTCT	960
TGGAAAGATA	CAGCTCCAGG	GTAAAGAGA	GAGTTTTAG	TGAAGTATCT	TTCAGATAGC	1020
AGGCAGGGAA	GCAATGTAGT	GTGGTGGGCA	GAGCCCCACA	CAGAACATCAGA	AGGGATGAAT	1080
GGATGTCCCA	GCCCAACCAC	TAATTCACTG	TATGGTCTTG	ATCTATTCT	TCTGTTTGA	1140

GAGCCTCCAG TTAAAATGGG GCTTCAGTAC CAGAGCAGCT AGCAACTCTG CCCTAATGGG	1200
AAATGAAGGG GAGCTGGGTG TGAGTGTGTTA CACTGTGCC TTCACGGGAT ACTTCTTTA	1260
TCTGCAGATG GCCTAATGCT TAGTTGTCCA AGTCGCGATC AAGGACTCTC TCACACAGGA	1320
AACTTCCCTA TACTGGCAGA TACACTTG TG ACTGAACCAT GCCCAGTTA TGCCTGTCTG	1380
ACTGTCACTC TGGCACTAGG AGGCTGATCT TGTACTCCAT ATGACCCCAC CCCTAGGAAC	1440
CCCCAGGGAA AACCAAGGCTC GGACAGCCCC CTGTTCTGA GATGGAAAGC ACAAATTAA	1500
TACACCACCA CAATGGAAAA CAAGTTCAAA GACTTTACT TACAGATCCT GGACAGAAAG	1560
GGCATAATGA GTCTGAAGGG CAGTCCTCCT TCTCCAGGTT ACATGAGGCA GGAATAAGAA	1620
GTCAGACAGA GACAGCAAGA CAGTTAACAA CGTAGGTTAA GAAATAGGGT GTGGTCACTC	1680
TCAATTCACT GGCAAATGCC TGAATGGTCT GTCTGAAGGA AGCAACAGAG AAGTGGGGAA	1740
TCCAGTCTGC TAGGCAGGAA AGATGCCTCT AAGTTCTTGT CTCTGGCCAG AGGTGTGGTA	1800
TAGAACCGAGA AACCCATATC AAGGGTGACT AAGCCGGCT TCCGGTATGA GAAATTAAAC	1860
TTGTATACAA AATGGTTGCC AAGGCAACAT AAAATTATAA GAATT	1906

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1619 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

GTCATGGAAT ACGCCTCTGA CGCTTCACTG GACCCCGAAG CCCC GTGGCC TCCC CGCGCC	60
CGCGCTCGCG CCTGCCCGGT ACTGCCTTGG GCCCTGGTCG CGGGGCTGCT GCTGCTGCTG	120
CTGCTCGCTG CCGCCTGCCG CGTCTTCCTC GCCTGCCCTC GGGCGTGTG CCGGGCTCGC	180
GCCTCGCCCG GCTCCCGGGC CAGCCCGAGA CTCCCGCAGG GTCCCGAGCT TTCGCCGAC	240
GATCCCGCCG GCCTCTTGGA CCTGCGGCAG GGCATGTTG CGCAGCTGGT GGCCAAAAT	300
GTTCTGCTGA TCGATGGGCC CCTGAGCTGG TACAGTGACC CAGGCCTGGC AGGC GTGTCC	360
CTGACGGGGG GCCTGAGCTA CAAAGAGGAC ACGAAGGAGC TGTTGGTGGC CAAGGCTGGA	420
GTC TACTATG TCTTCTTCA ACTAGAGCTG CGGCCGCTGG TGGCCGGCGA GGGCTCAGGC	480
TCCGTTTCAC TTGCGCTGCA CCTGCAGCCA CTGCGCTCTG CTGCTGGGC CGCCGCCCTG	540
GCTTGACCG TGGACCTGCC ACCCGCCTCC TCCGAGGCTC GGAAC TCGGC CTTCGGTTTC	600
CAGGGCCGCT TGCTGCACCT GAGTGCCGGC CAGGCCCTGG GCGTCCATCT TCACACTGAG	660
GCCAGGGCAC GCCATGCCTG GCAGCTTACC CAGGGCGCCA CAGTCTGGG ACTCTTCCGG	720
GTGACCCCCCG AAATCCCAGC CGGACTCCCT TCACCGAGGT CGGAATAACG CCCAGCCTGG	780
GTGCAGCCCA CCTGGACAGA GTCCGAATCC TACTCCATCC TTCATGGAGA CCCCTGGTGC	840
TGGGTCCCTG CTGCTTTCTC TACCTCAAGG GGCTTGGCAG GGGTCCCTGC TGCTGACCTC	900
CCCTTGAGGA CCCTCCTCAC CCACTCCTTC CCCAAGTTGG ACCTTGATAT TTATTCTGAG	960
CCTGAGCTCA GATAATATAT TATATATAT ATATATATAT ATATATTCT ATTAAAGAG	1020
GATCCTGAGT TTGTGAATGG ACTTTTTAG AGGAGTTGTT TTGGGGGGGG GGTCTTCGAC	1080
ATTGCCGAGG CTGGTCTTGA ACTCCTGGAC TTAGACGATC CTCCTGCCCT AGCCTCCCAA	1140
GCAACTGGGA TTCATCCTT CTATTAATTC ATTGTACTTA TTTGCCTATT TGTGTGTATT	1200
GAGCATCTGT AATGTGCCAG CATTGTGCC AGGCTAGGGG GCTATAGAAA CATCTAGAAA	1260
TAGACTGAAA GAAAATCTGA GTTATGGTAA TACGTGAGGA ATTTAAAGAC TCATCCCCAG	1320
CCTCCACCTC CTGTGTGATA CTTGGGGGCT AGCTTTTTC TTTCTTTCTT TTTTTGAGA	1380

TGGTCTTGTT	CTGTCAACCA	GGCTAGAATG	CAGCGGTGCA	ATCATGAGTC	AATGCAGCCT	1440
CCAGCCTCGA	CCTCCCGAGG	CTCAGGTGAT	CCTCCCATCT	CAGCCTCTCG	AGTAGCTGGG	1500
ACCACAGTTG	TGTGCCACCA	CACTTGGCTA	ACTTTTAAT	TTTTTGCGG	AGACGGTATT	1560
GCTATGTTGC	CAAGGTTGTT	TACATGCCAG	TACAATTAT	AATAAACACT	CATTTTCC	1619

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1239 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

AGCCTATAAA	GCACGGGCAC	TGGCGGGAGA	CGTGCACTGA	CCGACCGTGG	TAATGGACCA	60
GCACACACTT	GATGTGGAGG	ATACCGCGGA	TGCCAGACAT	CCAGCAGGTA	CTTCGTGCC	120
CTCGGATGCG	GCGCTCCTCA	GAGATAACCGG	GCTCCTCGCG	GACGCTGCGC	TCCTCTCAGA	180
TACTGTGCGC	CCCACAAATG	CCGCGCTCCC	CACGGATGCT	GCCTACCCCTG	CGGTTAATGT	240
TCGGGATCGC	GAGGCCGCGT	GGCCGCTGCG	ACTGAACCTTC	TGTTCCCGCC	ACCCAAAGCT	300
CTATGGCCTA	GTCGCTTGG	TTTGCTGCT	TCTGATGCC	GCCTGTGTT	CTATCTTCAC	360
CCGCACCGAG	CCTCGGCCAG	CGCTCACAAAT	CACCAACCTCG	CCCAACCTGG	GTACCCGAGA	420
GAATAATGCA	GACCAGGTCA	CCCCCTGTTTC	CCACATTGGC	TGCCCCAACAA	CTACACAAACA	480
GGGCTCTCCT	GTGTTCGCCA	AGCTACTGGC	AAAAAACCAA	GCATCGTTGT	GCAATACAAC	540
TCTGAACTGG	CACAGCCAAG	ATGGAGCTGG	GAGCTCATAAC	CTATCTCAAG	GTCTGAGGTA	600
CGAAGAAGAC	AAAAAGGAGT	TGGTGGTAGA	CAGTCCCGGG	CTCTACTACG	TATTTTGGA	660
ACTGAAGCTC	AGTCCAACAT	TCACAAACAC	AGGCCACAAG	GTGCAGGGCT	GGGTCTCTCT	720
TGTTTGCAA	GCAAAGCCTC	AGGTAGATGA	CTTGACAAC	TTGGCCCTGA	CAGTGGAACT	780
GTTCCCTTGC	TCCATGGAGA	ACAAGTTAGT	GGACCGTTCC	TGGAGTCAAC	TGTTGCTCCT	840
GAAGGCTGGC	CACCGCCTCA	GTGTGGGTCT	GAGGGCTTAT	CTGCATGGAG	CCCAGGATGC	900
ATACAGAGAC	TGGGAGCTGT	CTTATCCCAA	CACCACCAAG	TTTGGACTCT	TTCTGTGAA	960
ACCCGACAAC	CCATGGGAAT	GAGAACTATC	CTTCTTGTGA	CTCCTAGTTG	CTAAGTCCTC	1020
AAGCTGCTAT	GTTTTATGGG	GTCTGAGCAG	GGGTCCCTTC	CATGACTTT	TCTTGTCTTT	1080
AACTGGACTT	GGTATTATT	CTGAGCATAG	CTCAGACAAG	ACTTTATATA	ATTCACTAGA	1140
TAGCATTAGT	AAACTGCTGG	GCAGCTGCTA	GATAAAAAAA	AATTCTAAA	TCAAAGTTA	1200
TATTTATATT	AATATATAAA	AATAATGTG	TTTGTAAAT			1239

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 606 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

ATGATCGAAA CATAACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
ATGAAAATTT TTATGTATTT ACTTACTGTT TTTCTTATCA CCCAGATGAT TGGGTCAAGCA	120
CTTTTGCTG TGTATCGCTT CGCACAGGGCT TTTGAAATGC AAAAAGGTGA TCAGAACCT	180
CAAATTGCGG CACATGTCAT AAGTGAGGCC AGCAGTAAAA CAACATCTGT GTTACAGTGG	240
GCTGAAAAAG GATACTACAC CATGAGCAAC AACTTGGTAA CCCTGGAAAA TGGGAAACAG	300
CTGACCGTTA AAAGACAAGG ACTCTATTAT ATCTATGCCA AAGTCACCTT CTGTTCCAAT	360
CGGGAAGCTT CGAGTCAGC TCCATTATAA GCCAGCCTCT GCCTAAAGTC CCCCCGGTAGA	420
TTCGAGAGAA TCTTACTCAG AGCTGCAAAT ACCCACAGTT CCGCCAAACC TTGCGGGCAA	480
CAATCCATTC ACTTGGGAGG AGTATTGAA TTGCAACCA G TGCTTCGGT GTTTGTCAAT	540
GTGACTGATC CAAGCCAAGT GAGCCATGGC ACTGGCTTCA CGTCCTTTGG CTTACTCAA	600
CTCTGA	606

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 783 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

ATGATCGAAA CATAACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
ATGAAAATTT TTATGTATTT ACTTACTGTT TTTCTTATCA CCCAGATGAT TGGGTCAAGCA	120
CTTTTGCTG TGTATCTTCA TAGAAGATTG GATAAGGTCG AAGAGGAAGT AAACCTTCAT	180
GAAGATTTG TATTCTAAA AAAGCTAAAG AGATGCAACA AAGGAGAAGG ATCTTTATCC	240
TTGCTGAACG GTGAGGAGAT GAGAAGGCAA TTTGAAGACC TTGTCAGGA TATAACGTTA	300
AACAAAGAAG AGAAAAAAGA AAACAGCTTT GAAATGCAA AAGGTGATCA GAATCCTCAA	360
ATTGCGGCAC ATGTCATAAG TGAGGCCAGC AGTAAAACAA CATCTGTGTT ACAGTGGGCT	420
GAAAAAGGAT ACTACACCAT GAGCAACAAAC TTGGTAACCC TGGAAAATGG GAAACAGCTG	480
ACCGTTAAAA GACAAGGACT CTATTATATC TATGCCAAG TCACCTCTG TTCCAATCGG	540
GAAGCTCGA GTCAAGCTCC ATTATAGCC AGCCTCTGCC TAAAGTCCCC CGGTAGATT	600
GAGAGAATCT TACTCAGAGC TGCAAATACC CACAGTCCG CCAAACCTTG CGGGCAACAA	660
TCCATTCACT TGGGAGGAGT ATTGAATTG CAACCAGGTG CTTCGGTGTG TGTCATGTG	720
ACTGATCCAA GCCAAGTGAG CCATGGCACT GGCTTCACGT CCTTGGCTT ACTCAAAC	780
TGA	783

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 558 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

CTGCTGCACT	TCGGGGTAAT	CGGCCCCAG	AGGGAAAGAGC	AGTCCCCAGG	TGGCCCCTCC	60
ATCAACAGCC	CTCTGGTCA	AACACTCAGG	TCCTCTTCTC	AAGCCTCAAG	TAACAAGCCG	120
GTAGCCCACG	TTGTAGCCGA	CATCAACTCT	CCGGGGCAGC	TCCGGTGGTG	GGACTCGTAT	180
GCCAATGCC	TCATGGCCAA	CGGTGTGAAG	CTGGAAGACA	ACCAGCTGGT	GGTGCCTGCT	240
GACGGGCTTT	ACCTCATCTA	CTCACAGGTC	CTCTTCAGGG	GCCAAGGCTG	CCCTTCCACC	300
CCCTTGTTC	TCACCCACAC	CATCAGCCGC	ATTGCAGTCT	CCTACCAGAC	CAAGGTCAAC	360
ATCCTGTCTG	CCATCAAGAG	CCCTTGCCAC	AGGGAGACCC	CAGAGTGGGC	TGAGGCCAAG	420
CCCTGGTACG	AACCCATCTA	CCAGGGAGGA	GTCTTCCAGC	TGGAGAAGGG	AGATCGCCTC	480
AGTGCTGAGA	TCAACCTGCC	GGACTACCTG	GACTATGCCG	AGTCCGGCA	GGTCTACTTT	540
GGGATCATTG	CCCTGTGA					558

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	1783 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

CAAGTCACAT	GATCCAGGAT	GCAGGGAAA	ATCCTCTTG	GAACAGAGCT	GGGTACAGAA	60
CCGAATCAGA	TGAGGAGAGA	TAAGGTGTGA	TGTGGGACAG	ACTATATAAA	GCATGGAGCC	120
AGGGCTGCAA	CAAGCAGGCA	GCTGTGGGGC	TCCTTCCCCT	GACCCAGCCA	TGCAGGTGCA	180
GCCC GGCTCG	GTAGCCAGCC	CCTGGAGAAC	CACGAGGCC	TGGAGAAGCA	CAAGTCGCAG	240
CTACTTCTAC	CTCAGCACCA	CCGCACTGGT	GTGCCCTGTT	GTGGCAGTGG	CGATCATTCT	300
GGTACTGGTA	GTCCAGAAAA	AGGACTCCAC	TCCAAATACA	ACTGAGAAGG	CCCCCCTTAA	360
AGGAGGAAAT	TGCTCAGAGG	ATCTCTTCTG	TACCCCTGAA	AGTACTCCAT	CCAAGAAGTC	420
ATGGGCCTAC	CTCCAAGTGT	CAAAGCATCT	CAACAATACC	AAACTGTCT	GGAAAGAAGA	480
TGGCACCATC	CACGGACTCA	TATACCAGGA	CGGGAACCTG	ATAGTCCAAT	TCCCTGGCTT	540
GTACTTCATC	GTGTTGCCAAC	TGCAGTTCT	CGTGCAGTGC	TCAAATCATT	CTGTGGACCT	600
GACATTGCAG	CTCCTCATCA	ATTCCAAGAT	CAAAAAGCAG	ACGTTGGTAA	CAGTGTGTGA	660
GTCTGGAGTT	CAGAGTAAGA	ACATCTACCA	GAATCTCTCT	CAGTTTTGC	TGCATTACTT	720
ACAGGTCAAC	TCTACCATAT	CAGTCAGGGT	GGATAATTTC	CAGTATGTGG	ATACAAACAC	780
TTTCCCTCTT	GATAATGTGC	TATCCGTCTT	CTTATATAGT	AGCTCAGACT	GAATAGTTGT	840
TCTTAACCTT	TATGAAAATG	CTGTCTACCA	TACAGTACTT	CATCTGTCCA	AACATGGGCC	900
AAAGAAAATA	TTAGGACAAC	TCAAACTAAG	CATGTGAGTT	AGTGCACCTTC	TCTTTCTGTC	960
CTTTGGAAAA	ATACAAACCC	AGGATTAGA	AAAGTGGAGTC	TCCTTCAGAT	GCACAAACAG	1020
GAAAGAATGT	GATATGTGCA	CAGAGACCTA	CTTGGGCACT	AGAAGGGGTG	TGAGTTGTCC	1080
CAGTATAACC	ACTAATTCAAC	TGACCTTGAG	CCATTCTTCC	TTCCCCCTGG	AACTTGGGGT	1140
CTGAATCTGG	AAAAGTAGGA	GATGAGATT	ACATTTCCCC	AATATTTCT	TCAACTCAGA	1200
AGACGAGACT	GTGGAGCTGA	GCTCCCTACA	CAGATGAAGG	CCTCCCATGG	CATGAGGAAA	1260

ATGATGGTAC CAGTAATGTC TGTCTGACTG TCATCTCAGC AAGTCCTAAG GACTTCATG	1320
CTGCCTTGTT GAAAGATACT CTAACCTCTT GTAATGGCA AAGTGATCCT GTCTCTCACT	1380
GAGGGGAGTA GCTGCTGCCA TCTCCTGAGA CATACATGGA GACATTTCT GCCTCAAATTC	1440
CATTCTGTGT GCAGTTTTA AGTATTCCCC CAAAAGTTCT TGACAATGAG AACTTGAAAT	1500
GTGGGAAGAG CTTCTGGACA GCAAACATTA ACAGCTTCTC CTGACCAGAG AGACCATGCA	1560
AGCTTGGTCT TAGACCCATC AAGCTTGAGG TTTCTACATT GTGGGAGACA GACTTTGAC	1620
AAACCATTTG AGTTGATGTC TGGGCCCTG GGAGTTCTCC TTCAGTAAGG AGAGCAAGCC	1680
GTTCTAGTGC TGTGTCAGAG GATGGAGTAA AATAGACACT TTTCTGAAGG AAAGGAGAAC	1740
AAAGTTCCAG AAAAAGGCTA GAAAATGTTT AAAAAGAAAA AAA	1783

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	1047 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

AGAGAGCGCT GGGAGCCGGA GGGGAGCCGA GCGAGTTTG GCCAGTGGTC GTGCAGTCCA	60
AGGGGCTGGA TGGCATGCTG GACCCAAGCT CAGCTCAGCG TCCGGACCCA ATAACAGTTT	120
TACCAAGGGA GCAGCTTCT ATCCTGGCCA CACTGAGGTG CATAGCGTAA TGTCCATGTT	180
GTTCTACACT CTGATCACAG CTTTCTGAT CGGCATACAG GCGGAACCCAC ACTCAGAGAG	240
CAATGTCCCT GCAGGACACA CCATCCCCCA AGTCCACTGG ACTAAACTTC AGCATTCCCT	300
TGACACTGCC CTTCGCAGAG CCCGCAGCGC CCCGGCAGCG GCGATAGCTG CACCGCTGGC	360
GGGGCAGACC CGAACATTA CTGTGGACCC CAGGCTGTTT AAAAAGCGGC GACTCCGTT	420
ACCCCGTGTG CTGTTTAGCA CCCAGCCTCC CGTGAAGCT GCAGACACTC AGGATCTGGA	480
CTTCGAGGTC GGTGGTGCTG CCCCCTTCAA CAGGACTCAC AGGAGCAAGC GGTCATCATC	540
CCATCCCACATC TTCCACAGGG CGAATTCTC GGTGTGTGAC AGTGTCAAGCG TGTGGGTTGG	600
GGATAAGACC ACCGCCACAG ACATCAAGGG CAAGGAGGTG ATGGTGTGTT GAGAGGTGAA	660
CATTAACAAAC AGTGTATTCA AACAGTACTT TTTTGAGACC AAGTGCCTGG ACCCAAATCC	720
CGTTGACAGC GGGTGCCGGG GCATTGACTC AAAGCACTGG AACTCATATT GTACCACGAC	780
TCACACCTTT GTCAAGGCAGC TGACCATGGA TGGCAAGCAG GCTGCCTGGC GGTTTATCCG	840
GATAGATACG GCCTGTGTGT GTGTGCTCAG CAGGAAGGCT GTGAGAAGAG CCTGACCTGC	900
CGACACGCTC CCTCCCCCTG CCCCTCTAC ACTCTCCTGG GCCCCTCCCT ACCTCAACCT	960
GTAAATTATT TTAAATTATA AGGACTGCAT GGTAATTAT AGTTTATACA GTTTAAAGA	1020
ATCATTATT ATTAAATT TTGGAAGC	1047

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	1176 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GAGCGCCTGG	AGCCGGAGGG	GAGCGCATCG	AGTGACTTTG	GAGCTGGCCT	TATATTGGA	60
TCTCCCGGGC	AGCTTTTGG	AAACTCCTAG	TGAACATGCT	GTGCCTCAAG	CCAGTGAAAT	120
TAGGCTCCCT	GGAGGTGGGA	CACGGGCAGC	ATGGTGGAGT	TTTGGCCTGT	GGTCGTGCAG	180
TCCAGGGGGC	TGGATGGCAT	GCTGGACCCA	AGCTCACCTC	AGTGTCTGGG	CCCAATAAAG	240
GTTCAGCCAA	GGACGCAGCT	TTCTATACTG	GCCGCAGTGA	GGTGCATAGC	GTAATGTCCA	300
TGTTGTTCTA	CACTCTGATC	ACTGCGTTT	TGATCGGCGT	ACAGGCAGAA	CCGTACACAG	360
ATAGCAATGT	CCCAGAAGGA	GACTCTGTCC	CTGAAGCCCCA	CTGGACTAAA	CTTCAGCATT	420
CCCTTGACAC	AGCCCTCCGC	AGAGCCCGCA	GTGCCCTAC	TGCACCAATA	GCTGCCGAG	480
TGACAGGGCA	GACCCGCAAC	ATCACTGTAG	ACCCCAGACT	GTAAAGAAA	CGGAGACTCC	540
ACTCACCCCG	TGTGCTGTT	AGCACCCAGC	CTCCACCCAC	CTCTTCAGAC	ACTCTGGATC	600
TAGACTTCCA	GGCCCATGGT	ACAATCCCTT	TCAACAGGAC	TCACCGGAGC	AAGCGCTCAT	660
CCACCCCACCC	AGTCTTCCAC	ATGGGGGAGT	TCTCAGTGTG	TGACAGTGTC	AGTGTGTGGG	720
TTGGAGATAA	GACCACAGCC	ACAGACATCA	AGGGCAAGGA	GGTGACAGTG	CTGGCCGAGG	780
TGAACATTAA	CAACAGTGT	TTCAGACAGT	ACTTTTTGA	GACCAAGTGC	CGAGCCTCCA	840
ATCCTGTTGA	GAGTGGGTGC	CGGGGCATCG	ACTCCAAACA	CTGGAACTCA	TACTGCACCA	900
CGACTCACAC	CTTCGTCAAG	GGTTGACAA	CAGATGAGAA	GCAGGCTGCC	TGGAGGTTCA	960
TCCGGATAGA	CACAGCCTGT	GTGTGTGTGC	TCAGCAGGAA	GGCTACAAGA	AGAGGCTGAC	1020
TTGCCTGCAG	CCCCCTTCCC	CACCTGCCCC	CTCCACACTC	TCTTGGGCC	CTCCCTACCT	1080
CAGCTGTAA	ATTATTTAA	ATTATAAGGA	CTGCATGATA	ATTATCGTT	TATACAATTT	1140
TAAAGACATT	ATTTATTAAA	TTTCAAAGC	ATCCTG			1176

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	1623 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

TCAGAGTCCT	GTCCITGACA	CTTCAGTCCTC	CACAAGACTG	AGAGGAGGAA	ACCCCTTCCT	60
GGGGCTGGGT	GCCATGCGAGC	AGCCC GTGAA	TTACCCATGT	CCCCAGATCT	ACTGGGTAGA	120
CAGCAGTGCC	ACTTCTCCTT	GGGCTCCTCC	AGGGTCAGTT	TTTTCTTGTG	CATCCTCTGG	180
GCTTAGAGGG	CCAGGACAAA	GGAGACCACC	GCCTCCACCA	CCACCTCCAT	CACCACTACC	240
ACCGCCTTCC	CAACCACCCC	CGCTGCCCTC	ACTAAGCCCT	CTAAAGAAGA	AGGACAACAT	300
AGAGCTGTGG	CTACCGGTGA	TATTTTCTAT	GGTGCTGGTG	GCTCTGGTTG	GAATGGGGTT	360
AGGAATGTAT	CAACTCTTTC	ATCTACAGAA	GGAACTGGCA	GAACTCCGTG	AGTCACCAA	420
CCACAGCCTT	AGAGTATCAT	CTTTGAAAAA	GCAAATAGCC	AACCCCAGCA	CACCTCTGA	480
AACCAAAAAG	CCAAGGAGTG	TGGCCCACCTT	AACAGGGAAC	CCCGCTCAA	GGTCATCCC	540
TCTGGAATGG	GAAGACACAT	ATGGAACTGC	TTTGATCTCT	GGAGTGAAGT	ATAAGAAAGG	600
CGGCCTTGTG	ATCAATGAGG	CTGGGTTGTA	CTTCGTATAT	TCCAAAGTAT	ACTTCCGGGG	660

TCAGTCTTGC AACAGCCAGC CCCTAAGCCA CAAGGTCTAT ATGAGGAAC TTAAGTATCC	720
TGGGGATCTG GTGCTAATGG AGGAGAAGAA GTTGAATTAC TGCACTACTG GCCAGATATG	780
GGCCCACAGC AGCTACCTAG GGGCAGTATT TAATCTTACC GTTGCTGACC ATTTATATGT	840
CAACATATCT CAACTCTCTC TGATCAATT TGAGGAATCT AAGACCTTT TTGGCTTATA	900
TAAGCTTTAA AGGAAAAAGC ATTTAGAAT GATCTATTAT TCTTTATCAT GGATGCCAGG	960
AATATTGTCT TCAATGAGAG TCTTCTTAAG ACCAATTGAG CCACAAAGAC CACAAGGTCC	1020
AACAGGTCAAG CTACCCCTCA TTTTCTAGAG GTCCATGGAG TGGTCCTTAA TGCCTGCATC	1080
ATGAGCCAGA TGGGAAGAAG ACTGTTCCCTG AGGAACATAA AGTTTTGGC TGCTGTGTGG	1140
CAATGCAGAG GCAAAGAGAA GGAACGTGCT GATGTTAAAT GGCCAAGAGC ATTTAGCCA	1200
TTGAAGAAAA AAAAACCTT TAAACTCACC TTCCAGGGTG GGTCTACTTG CTACCTCACA	1260
GGAGGCCGTC TTTTAGACAC ATGGTTGTGG TATGACTATA CAAGGGTGAG AAAGGATGCT	1320
AGGTTTCATG GATAAGCTAG AGACTGAAAA AAGCCAGTGT CCCATTGGCA TCATCTTAT	1380
TTTTAACTGA TGTTTCTGA GCCCACCTT GATGCTAACCA GAGAAATAAG AGGGGTGTTT	1440
GAGGCACAAG TCATTCTCTA CATAGCATGT GTACCTCCAG TGCAATGATG TCTGTGTGTG	1500
TTTTTATGTA TGAGAGTACA GCGATTCTAA AGAGTCACAT GAGTACAACG CGTACATTAC	1560
GGAGTACATA TTAGAACGT ATGTGTTACA TTTGATGCTA GAATATCTGA ATGTTTCTTG	1620
CTA	1623

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GTTAAGCTTT TCAGTCAGCA TGATAGAA

28

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GTTTCTAGAT CAGAGTTTGA GTAAGCC

27

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

CCAAGACTAG TTAACACAGC ATGATCGAAA

30

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

CCAATGCGGC CGCACTCAGA ATTCAACCTG

30

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 972 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

TCTAGACTCA GGACTGAGAA GAAGTAAAC CGTTGCTGG GGCTGGCCTG ACTCACCGAC	60
TGCCATGCAG CAGCCCTTCA ATTACCCATA TCCCCAGATC TACTGGGTGG ACAGCAGTGC	120
CAGCTCTCCC TGGGCCCTC CAGGCACAGT TCTTCCTGT CCAACCTCTG TGCCCAGAAG	180
GCCTGGTCAA AGGAGGCCAC CACCACCACC GCCACCGCCA CCACTACCAC CTCCGCCGCC	240
GCCGCCACCA CTGCCTCCAC TACCGCTGCC ACCCCTGAAG AAGAGAGGGA ACCACAGCAC	300
AGGCCTGTGT CTCCCTGTGA TGTTCATGGTCTGGTT GCCTGGTAG GATTGGGCCT	360
GGGGATGTTT CAGCTCTTCC ACCTACAGAA GGAGCTGGCA GAACTCCGAG AGTCTACCAG	420
CCAGATGCAC ACAGCATCAT CTTGGAGAA GCAAATAGGC CACCCAGTC CACCCCTGA	480

AAAAAAAGGAG	CTGAGGAAAG	TGGCCCATTT	AACAGGCAAG	TCCAACCTCAA	GGTCCATGCC	540
TCTGGAATGG	GAAGACACCT	ATGGAATTGT	CCTGCTTCT	GGAGTGAAGT	ATAAGAAGGG	600
TGGCCTTGTG	ATCAATGAAA	CTGGGCTGTA	CTTGTATAT	TCCAAAGTAT	ACTTCCGGGG	660
TCAATCTTGC	AACAACCTGC	CCCTGAGCCA	CAAGGTCTAC	ATGAGGAACT	CTAAGTATCC	720
CCAGGATCTG	GTCATGATGG	AGGGGAAGAT	GATGAGCTAC	TGCACTACTG	GGCAGATGTG	780
GGCCCGCAGC	AGCTACCTGG	GGGCAGTGTGTT	CAATCTTACC	AGTGCTGATC	ATTATATATGT	840
CAACGTATCT	GAGCTCTCTC	TGGTCAATT	TGAGGAATCT	CAGACGTTTT	TCGGCTTATA	900
TAAGCTCTAA	GAGAAGCACT	TTGGGATTCT	TTCCATTATG	ATTCTTGTGTT	ACAGGCACCG	960
AGATGTTCTA	GA					972

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	885 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

ATGCAGCAGC	CCATGAATTA	CCCATGTCCC	CAGATCTTCT	GGGTAGACAG	CAGTGCCACT	60
TCATCTTGGG	CTCCTCCAGG	GTCAGTTTTT	CCCTGTCCAT	CTTGTGGGCC	TAGAGGGCCG	120
GACCAAAGGA	GACCGCCACC	TCCACCACCA	CCTGTGTCAC	CACTACCACC	GCCATCACAA	180
CCACTCCAC	TGCCGCCACT	GACCCCTCTA	AAGAAGAAGG	ACCAACAACAC	AAATCTGTGG	240
CTACCGGTGG	TATTTTCAT	GGTTCTGGTG	GCTCTGGTTG	GAATGGGATT	AGGAATGTAT	300
CAGCTCTTCC	ACCTGCAGAA	GGAAGTGGCA	GAACTCCGTG	AGTCACCAA	CCAAAGCCTT	360
AAAGTATCAT	CTTTTGAAAA	GCAAATAGCC	AACCCAGTA	CACCCCTCTGA	AAAAAAAGAG	420
CCGAGGAGTG	TGGCCCATTT	AACAGGGAAC	CCCCACTCAA	GGTCCATCCC	TCTGGAATGG	480
GAAGACACAT	ATGGAACCGC	TCTGATCTCT	GGAGTGAAGT	ATAAGAAAGG	TGGCCTTGTG	540
ATCAACGAAG	CTGGGTTGTA	CTTCGTATAT	TCCAAAGTAT	ACTTCCGGGG	TCAGTCTTGC	600
AACAACCAGC	CCCTAAACCA	CAAGGTCTAT	ATGAGGAACT	CTAAGTATCC	TGGGGATCTG	660
GTGCTAATGG	AGGAGAAGAG	GTTGAACTAC	TGCACTACTG	GACAGATATG	GGCCCACAGC	720
AGCTACCTGG	GGGCAGTATT	CAATCTTACC	AGTGCTGACC	ATTATATATGT	CAACATATCT	780
CAACTCTCTC	TGATCAATT	TGAGGAATCT	AAGACCTTTT	TCGGCTTGTGTA	TAAGCTTTAA	840
AAGAAAAAGC	ATTTTAAAAT	GATCTACTAT	TCTTTATCAT	GGGCA		885

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	29 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

CTTAAGCTTC TACAGGACTG AGAAGAAGT

29

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

CTTGÀATTCC AACATTCTCG GTGCCTGTAA

27

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

TCAGGATCCA CAAGGCTGTG AGAAGGA

27

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

CTTGTCTAGA CCTGGTGCC CATGATA

27

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	680 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

ATGCCGGAGG AAGGTCGCC	TTGCCCTGG GTTCGCTGGA	GCGGGACCGC GTTCCAGCGC	60
CAATGGCCAT GGCTGCTGCT	GGTGGTGT	TTACTGTGT TTTGCTGTTG	120
AGCGGACTAC TCAGTAAGCA	GCAACAGAGG CTGCTGGAGC	ACCCTGAGCC GCACACAGCT	180
GAGTTACAGC TGAATCTCAC	AGTCCTCGG AAGGACCCA	CACTGCGCTG GGGAGCAGGC	240
CCAGCCCTTGG GAAGGTCTT	CACACACGGA CCAGAGCTGG	AGGAGGGCCA TCTGCGTATC	300
CATCAAGATG GCCTCTACAG	GCTGCATATC CAGGTGACAC	TGGCCAAGTG CTCTTCCCCA	360
GGCAGCACCC TGCAAGCACAG	GGCCACCCCTG GCTGTGGGCA	TCTGCTCCCC CGCTGCGCAC	420
GGCATCAGCT TGCTGCGTGG	GGCCTTTGGA CAGGACTGTA	CAGTGGCATT ACAGGCCTG	480
ACATACCTGG TCCACGGAGA	TGTCCTCTGT ACCAACCTCA	CCCTGCCTCT GCTGCCGTCC	540
CGCAACGCTG ATGAGACCTT	CTTGGAGTT CAGTGGATAT	GCCCTTGACC ACAACTCCAG	600
GATGACTTGT GAATATTTT	TTTCTTTCA AGTTCTACGT	ATTATAAAAT GTATATAGTA	660
CACATAAAAA AAAAAAAA			680

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	846 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

ATGCAGCAGC CCTTCAATTA	CCCATATCCC CAGATCTACT	GGGTGGACAG CAGTGCCAGC	60
TCTCCCTGGG CCCCTCCAGG	CACAGTTCTT CCCTGTCCAA	CCTCTGTGCC CAGAAGGCCT	120
GGTCAAAGGA GGCCACCAACC	ACCACCGCCA CCGCCACAC	TACCACCTCC GCGCCGCCG	180
CCACCACTGC CTCCACTACC	GCTGCCACCC CTGAAGAAGA	GAGGGAACCA CAGCACAGGC	240
CTGTGTCTCC TTGTGATGTT	TTTCATGGTT CTGGTGCCT	TGGTAGGATT GGGCCTGGGG	300
ATGTTTCAGC TCTTCCACCT	GCAGAAGGAA CTGGCAGAAC	TCCGTGAGTT CACCAACCAA	360
AGCCTAAAG TATCATCTT	TGAAAAGCAA ATAGGCCACC	CCAGTCCACC CCCTGAAAAA	420
AAGGAGCTGA GGAAAGTGGC	CCATTTAACCA GGCAAGTCCA	ACTCAAGGTC CATGCCCTTG	480
GAATGGGAAG ACACCTATGG	AATTGTCCTG CTTTCTGGAG	TGAAGTATAA GAAGGGTGGC	540
CTTGTGATCA ATGAAACTGG	GCTGTACTTT GTATATTCCA	AAGTATAACTT CGGGGTCAA	600
TCTTGCAACA ACCTGCCCT	GAGCCACAAG GTCTACATGA	GGAACTCTAA GTATCCCCAG	660

GATCTGGTGA TGATGGAGGG GAAGATGATG AGCTACTGCA CTACTGGGCA GATGTGGGCC	720
CGCAGCAGCT ACCTGGGGC AGTGTCAAT CTTACCAGTG CTGATCATT ATATGTCAAC	780
GTATCTGAGC TCTCTCTGGT CAATTTGAG GAATCTCAGA CGTTTTTCGG CTTATATAAG	840
CTCTAA	846

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 786 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

ATGCAGCAGC CCTTCAATTA CCCATATCCC CAGATCTACT GGGTGGACAG CAGTGCCAGC	60
TCTCCCTGGG CCCCTCCAGG CACAGTTCTT CCCTGTCCAA CCTCTGTGCC CAGAAGGCCT	120
GGTCAAAGGA GGCCACCACC ACCACCGCCA CCGCCACAC TACCACCTCC GCCGCCGCCG	180
CCACCACTGC CTCCACTACC GCTGCCACCC CTGAAGAAGA GAGGGAACCA CAGCACAGGC	240
CTGTGTCTCC TTGTGATGTT TTTCATGGTT CTGGTTGCCT TGGTAGGATT GGGCTGGGG	300
ATGTTTCAGC TCTTCCGCTT CGCACAGGCT ATAGGCCACC CCAGTCCACC CCCTGAAAAA	360
AAGGAGCTGA GGAAAGTGGC CCATTTAACCA GGCAAGTCCA ACTCAAGGTC CATGCCCTTG	420
GAATGGGAAG ACACCTATGG AATTGTCCTG CTTTCTGGAG TGAAGTATAA GAAGGGTGGC	480
CTTGTGATCA ATGAAACTGG GCTGTACTTT GTATATTCCA AAGTATACTT CCGGGGTCAA	540
TCTTGCAACA ACCTGCCCT GAGCCACAAG GTCTACATGA GGAACTCTAA GTATCCCCAG	600
GATCTGGTGA TGATGGAGGG GAAGATGATG AGCTACTGCA CTACTGGGCA GATGTGGGCC	660
CGCAGCAGCT ACCTGGGGC AGTGTCAAT CTTACCAGTG CTGATCATT ATATGTCAAC	720
GTATCTGAGC TCTCTCTGGT CAATTTGAG GAATCTCAGA CGTTTTTCGG CTTATATAAG	780
CTCTAA	786

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 864 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

ATGCAGCAGC CCTTCAATTA CCCATATCCC CAGATCTACT GGGTGGACAG CAGTGCCAGC	60
TCTCCCTGGG CCCCTCCAGG CACAGTTCTT CCCTGTCCAA CCTCTGTGCC CAGAAGGCCT	120
GGTCAAAGGA GGCCACCACC ACCACCGCCA CCGCCACAC TACCACCTCC GCCGCCGCCG	180
CCACCACTGC CTCCACTACC GCTGCCACCC CTGAAGAAGA GAGGGAACCA CAGCACAGGC	240

CTGTGTCTCC	TTGTGATGTT	TTTCATGGTT	CTGGTTGCCT	TGGTAGGATT	GGGCCTGGGG	300
ATGTTTCAGC	TCTTCCAATC	CTCCATCCTC	CCCTATGCCG	GAGGAGGGTT	CGGGCTGCTC	360
GGTGCAGCGC	AGGCCCTATG	GGTGCCTCCT	CGGGCCATCC	TCAATCCTAT	AGGCCACCCC	420
AGTCCACCCC	CTGAAAAAAA	GGAGCTGAGG	AAAGTGCCTC	ATTTAACAGG	CAAGTCCAAC	480
TCAAGGTCCA	TGCCTCTGGA	ATGGGAAGAC	ACCTATGGAA	TTGTCCTGCT	TTCTGGAGTG	540
AAGTATAAGA	AGGGTGGCCT	TGTGATCAAT	GAAACTGGGC	TGTACTTTGT	ATATTCCAAA	600
GTATACTTCC	GGGGTCAATC	TTGCAACAAC	CTGCCCCCTGA	GCCACAAGGT	CTACATGAGG	660
AACTCTAAGT	ATCCCCAGGA	TCTGGTGTATG	ATGGAGGGGA	AGATGATGAG	CTACTGCCT	720
ACTGGGCAGA	TGTGGGCCCG	CACAGCTAC	CTGGGGCAG	TGTTCAATCT	TACCAAGTGT	780
GATCATTAT	ATGTCAACGT	ATCTGAGCTC	TCTCTGGTCA	ATTTTGAGGA	ATCTCAGACG	840
TTTTTCGGCT	TATATAAGCT	CTAA				864

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 828 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

ATGCAGCAGC	CCTTCAATTA	CCCATATCCC	CAGATCTACT	GGGTGGACAG	CAGTGCCAGC	60
TCTCCCTGGG	CCCCTCCAGG	CACAGTTCTT	CCCTGTCCAA	CCTCTGTGCC	CAGAAGGCCT	120
GGTCAAAGGA	GGCCACCACC	ACCACCGCCA	CCGCCACCC	TACCACCTCC	GCCGCCGCCG	180
CCACCACTGC	CTCCACTACC	GCTGCCACCC	CTGAAGAAGA	GAGGGAACCA	CAGCACAGGC	240
CTGTGTCTCC	TTGTGATGTT	TTTCATGGTT	CTGGTTGCCT	TGGTAGGATT	GGGCCTGGGG	300
ATGTTTCAGC	TCTTCCACCT	ACAGCGAGAG	TCTACCAGCC	AGATGCACAC	AGCATCATCT	360
TTGGAGAAGC	AAATAGGCCA	CCCCAGTCCA	CCCCCTGAAA	AAAAGGAGCT	GAGGAAAGTG	420
GCCCATTAA	CAGGCAAGTC	CAACTCAAGG	TCCATGCCTC	TGGAATGGGA	AGACACCTAT	480
GGAATTGTCC	TGCTTTCTGG	AGTGAAGTAT	AAGAAGGGTG	GCCTTGAT	CAATGAAACT	540
GGGCTGTACT	TTGTATATTG	CAAAGTATAC	TTCCGGGGTC	AATCTTGCAA	CAACCTGCC	600
CTGAGGCCACA	AGGTCTACAT	GAGGAACACT	AAGTATCCCC	AGGATCTGGT	GATGATGGAG	660
GGGAAGATGA	TGAGCTACTG	CACTACTGGG	CAGATGTGGG	CCCGCAGCAG	CTACCTGGGG	720
GCAGTGTCA	ATCTTACCAAG	TGCTGATCAT	TTATATGTCA	ACGTATCTGA	GCTCTCTCTG	780
GTCAATTTCG	AGGAATCTCA	GACGTTTTTC	GGCTTATATA	AGCTCTAA		828

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 846 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

ATGGCTATGA	TGGAGGTCCA	GGGGGGACCC	AGCCTGGAC	AGACCTGCGT	GCTGATCGTG	60
ATCTTCACAG	TGCTCCTGCA	GTCTCTCTGT	GTGGCTGTAA	CTTACGTGTA	CTTTACCAAC	120
GAGCTGAAGC	AGATGCAGGA	CAAGTACTCC	AAAAGTGGCA	TTGCTTGTAA	CTTAAAAGAA	180
GATGACAGTT	ATTGGGACCC	CAATGACGAA	GAGAGTATGA	ACAGCCCCCTG	CTGGCAAGTC	240
AAGTGGCAAC	TCCGTCAGCT	CGTTAGAAAG	ATGATTTGA	GAACCTCTGA	GGAAACCATT	300
TCTACAGTTC	AAGAAAAGCA	ACAAAATATT	TCTCCCTAG	TGAGAGAAAG	AGGTCTTCAG	360
AGAGTAGCAG	CTCACATAAC	TGGGACCAGA	CGAAGAAGCA	ACACATTGTC	TTCTCCTAAC	420
TCCAAGAATG	AAAAGGCTCT	GGGCCGCAAA	ATAAAACCT	GGGAATCATC	AAGGAGTGGG	480
CATTCCATTCC	TGAGCAACTT	GCACCTGAGG	AATGGTGAAC	TGGTCATCCA	TGAAAAAGGG	540
TTTTACTACA	TCTATTCCCA	AACATACTTT	CGATTTCAGG	AGGAAATAAA	AGAAAACACA	600
AAGAACGACA	AACAAATGGT	CCAATATATT	TACAAATACA	CAAGTTATCC	TGACCCCTATA	660
TTGTTGATGA	AAAGTGTAG	AAATAGTTGT	TGGTCTAAAG	ATGCAGAATA	TGGACTCTAT	720
TCCATCTATC	AAGGGGAAAT	ATTGAGCTT	AAGGAAAATG	ACAGAAATTTC	TGTTTCTGTA	780
ACAAATGAGC	ACTTGATAGA	CATGGACCAT	GAAGCCAGTT	TTTCGGGGC	CTTTTTAGTT	840
GGCTAA						846

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	876 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

ATGCCCTCCT	CAGGGGCCCT	GAAGGACCTC	AGCTTCAGTC	AGCACTTCAG	GATGATGGTG	60
ATTTGCATAG	TGCTCCTGCA	GGTGCTCCTG	CAGGCTGTGT	CTGTGGCTGT	GACTTACATG	120
TACCTCACCA	ACGAGATGAA	GCAGCTGCAG	GACAATTACT	CCAAAATTGG	ACTAGCTTGC	180
TTCTCAAAGA	CGGATGAGGA	TTTCTGGGAC	TCCACTGATG	GAGAGATCTT	GAACAGACCC	240
TGCTTGCAGG	TTAAGAGGCA	ACTGTATCAG	CTCATTGAAG	AGGTGACTTT	GAGAACCTTT	300
CAGGACACCA	TTTCTACAGT	TCCAGAAAAG	CAGCTAAGTA	CTCCTCCCTT	GCCCAGAGGT	360
GGAAGACCTC	AGAAAGTGGC	AGCTCACATT	ACTGGGATCA	CTCGGAGAAG	CAACTCAGCT	420
TTAATTCCAA	TCTCCAAGGA	TGAAAGACCC	TTAGGCCAGA	AGATTGAATC	CTGGGAGTCC	480
TCTCGGAAAG	GGCATTCTATT	TCTCAACCAC	GTGCTCTTA	GGAATGGAGA	GCTGGTCATC	540
GAGCAGGAGG	GCCTGTATTA	CATCTATTCC	CAAACATACT	TCCGATTTCA	GGAAGCTGAA	600
GACGCCCTCA	AGATGGCTC	AAAGGACAAG	GTGAGAACCA	AACAGCTGGT	GCAGTACATC	660
TACAAGTACA	CCAGCTATCC	GGATCCCATA	GTGCTCATGA	AGAGCGCCAG	AAACAGCTGT	720
TGGTCCAGAG	ATGCCGAGTA	CGGACTGTAC	TCCATCTATC	AGGGAGGATT	GTTCGAGCTA	780
AAAAAAAATG	ACAGGATTTT	TGTTTCTGTG	ACAAATGAAC	ATTGTATGGA	CCTGGATCAA	840
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(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	720 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

ATGGAGCCAG GGCTGCAACA AGCAGGCAGC TGTGGGGCTC CTTCCCCCTGA CCCAGGCCATG	60
CAGGTGCAGC CGGGCTCGGT AGCCAGCCCC TGGAGAACGA CGAGGCCCTG GAGAACACACA	120
AGTCGCAGCT ACTTCTACCT CAGCACCAACC GCACTGGTGT GCCTTGTTGT GGCAGTGGCG	180
ATCATTCTGG TACTGGTAGT CCAGAAAAAG GACTCCACTC CAAATACAAAC TGAGAACGGCC	240
CCCCTTAAAG GAGGAAATTG CTCAGAGGAT CTCTTCTGTA CCCTGAAAAG TACTCCATCC	300
AAGAACATCAT GGGCCTACCT CCAAGTGTCA AAGCATCTCA ACAATACCAA ACTGTCATGG	360
AACGAAGATG GCACCATCCA CGGACTCTATA TACCAGGACG GGAACCTGAT AGTCCAATTC	420
CCTGGCTTGT ACTTCATCGT TTGCCAACTG CAGTTCTCG TGCACTGCTC AAATCATTCT	480
GTGGACCTGA CATTGCAGCT CCTCATCAAT TCCAAGATCA AAAAGCAGAC GTTGGTAACA	540
GTGTGTGAGT CTGGAGTTCA GAGTAAGAAC ATCTACCAAGA ATCTCTCTCA GTTTTGCTG	600
CATTACTTAC AGGTCAACTC TACCATATCA GTCAGGGTGG ATAATTCTCA GTATGTGGAT	660
ACAAACACTT TCCCTTTGA TAATGTGCTA TCCGTCTTCT TATATAGTAG CTCAGACTGA	720

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	930 base pairs
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

ATGGACCAGC ACACACTTGA TGTGGAGGAT ACCGGGGATG CCAGACATCC AGCAGGTACT	60
TCGTGCCCT CGGATGCGGC GCTCTCAGA GATACCGGGC TCCTCGCGGA CGCTCGCCTC	120
CTCTCAGATA CTGTGCGCCC CACAAATGCC GCGCTCCCCA CGGATGCTGC CTACCCCTGCG	180
GTTAATGTTG GGGATGCGA GGGCGCGTGG CCGCCTGCAC TGAACCTCTG TTCCCGCCAC	240
CCAAAGCTCT ATGGCCTAGT CGCTTGGTT TTGCTGCTTC TGATGCCGC CTGTGTTCCCT	300
ATCTTCACCC GCACCGAGCC TCGGCCAGCG CTCACAATCA CCACCTCGCC CAACCTGGGT	360
ACCCGAGAGA ATAATGCAGA CCAGGTCAACC CCTGTTCCC ACATTGGCTG CCCCCAACACT	420
ACACAACAGG GCTCTCCTGT GTTCGCAAG CTACTGGCTA AAAACCAAGC ATCGTTGTGC	480
AATACAACATC TGAACGGCA CAGCCAAGAT GGAGCTGGGA GCTCATACCT ATCTCAAGGT	540
CTGAGGTACG AAGAAGACAA AAAGGAGTTG GTGGTAGACA GTCCCGGGCT CTACTACGTA	600
TTTTGGAAC TGAAGCTCAG TCCAACATTC ACAAACACAG GCCACAAGGT GCAGGGCTGG	660

GTCTCTCTTG	TTTGCAAGC	AAAGCCTCAG	GTAGATGACT	TTGACAACCTT	GGCCCTGACA	720
GTGGAACGTG	TCCCTTGCTC	CATGGAGAAC	AAGTTAGTGG	ACCGTTCTG	GAGTCACAG	780
TTGCTCCTGA	AGGCTGGCCA	CCGCCTCAGT	GTGGGTCTGA	GGGCTTATCT	GCATGGAGCC	840
CAGGATGCAT	ACAGAGACTG	GGAGCTGTCT	TATCCAAACA	CCACCAGCTT	TGGACTCTTT	900
CTTGTGAAAC	CCGACAACCC	ATGGGAATGA				930

CLAIMS

1. A method of altering the immunoreactivity of human cells, which method comprising introducing a gene 5 encoding an accessory molecule ligand into said cells so that said accessory molecule ligand is expressed on the surface of said cells.

2. The method of claim 1 wherein the accessory molecule to which the accessory molecule ligand 10 specifically binds is also present on the surface of said human cells.

3. The method of claim 1 wherein said human cells are neoplastic human cells.

4. The method of claim 1 wherein said accessory 15 molecule ligand gene is a chimeric gene.

5. The method in claim 1 wherein said accessory molecule ligand gene is present in a vector capable of transducing human cells.

6. The method of claim 1 wherein said accessory 20 molecule ligand gene is present as part of a genetic vector.

7. The method of claim 1 wherein said accessory molecule ligand gene is operatively linked to a promoter region and a polyadenylation signal.

25 8. The method of claim 1 wherein said gene is a CD40 ligand gene.

9. The method of claim 7 wherein said CD40 ligand gene is a murine CD40 ligand gene.

10. The method of claim 4 wherein said gene is a 30 chimeric gene which comprises at least a portion of a murine CD40 ligand gene.

11. A method of treating a human neoplasia comprising inserting into said human neoplastic cells a gene which

encodes an accessory molecule ligand into said human neoplastic cells so that said accessory molecule ligand is expressed on the surface of said neoplastic cells.

12. The method of claim 11 further comprising:

5 a) obtaining said human neoplastic cells from a human patient;

b) infusing said human neoplastic cells after having inserted said accessory molecule ligand on the surface of said cells back into said patient.

10 13. The method of claim 11 wherein the accessory molecule to which the said accessory molecule ligand specifically binds is present on the surface of said human neoplastic cells.

14. The method of claim 11 wherein said accessory 15 molecule ligand gene is a chimeric gene.

15. The method of claim 11 wherein said accessory molecule ligand gene is a chimeric gene which contains at least a portion of the murine CD40 ligand gene.

16. The method of claim 11 wherein said accessory 20 molecule ligand gene is present as part of a genetic vector.

17. The method of claim 11 wherein said accessory molecule ligand gene is operatively linked to a promoter region and a 3' end region.

25 18. The method of claim 11 wherein said accessory molecule ligand gene is a CD40 ligand gene.

19. The method of claim 11 wherein the said CD40 ligand gene is a murine CD40 ligand gene.

20. The method of claim 11 wherein said accessory 30 molecule ligand gene is a Fas-ligand gene or a CD27 ligand gene.

21. The method of claim 11 wherein said accessory molecule ligand gene is present in a gene therapy vector.

22. A method of treating a neoplasia in a patient comprising injecting into the tumor bed of said patient a gene which encodes an accessory molecule ligand so that said accessory molecule ligand is expressed on the surface 5 of said tumor cells thereby causing said cells to participate in an immune reaction.

23. A gene therapy vector containing an accessory molecule ligand gene.

24. The gene therapy vector of claim 23 wherein said 10 accessory molecule gene is a CD40 ligand gene.

25. The gene therapy vector of claim 23 wherein said CD40 ligand gene is a murine CD40 ligand gene.

26. The gene therapy vector of claim 23 wherein said CD40 ligand gene is a chimeric gene.

27. The gene therapy vector of claim 23 wherein said 15 chimeric gene contains at least a portion of the murine CD40 ligand gene.

28. The gene therapy vector of claim 23 wherein at 20 least a portion of said vector is derived from adenovirus DNA.

29. The gene therapy vector of claim 23 wherein said vector contains at least a promoter region and a 3' end region.

30. The gene therapy vector of claim 23 wherein said 25 promoter region and said 3' end region are not derived from the same species from which the CD40 ligand gene is derived.

31. The gene therapy vector of claim 23 wherein said portion of said vector is derived from viral DNA.

30. 32. The gene therapy vector of claim 23 wherein at least a portion of said vector is derived from a retrovirus.

33. The gene therapy vector of claim 23 wherein said vector is capable of transducing human cells.

34. The gene therapy vector of claim 23 wherein said vector is capable of transducing animal cells.

5 35. The gene therapy vector of claim 23 wherein said human cells are human neoplastic cells.

36. The gene therapy vector of claim 23 wherein said human cells are human antigen presenting cells.

10 37. A genetic construct containing a promoter operatively linked to an accessory molecule ligand gene which is also operatively linked to a polyadenylation signal.

15 38. A genetic construct in which a promoter is operatively linked to a chimeric accessory molecule ligand gene and a polyadenylation signal.

39. A gene therapy vector containing a chimeric accessory molecule ligand gene.

20 40. The gene therapy vector of claim 39 wherein said chimeric accessory molecule ligand gene contains at least one gene segment derived from a murine CD40 ligand gene and other gene segments derived from other accessory molecule genes.

25 41. The gene therapy vector of claim 39 wherein said other accessory molecule ligand genes are human accessory molecule ligand genes.

42. The gene therapy vector of claim 39 wherein said human accessory molecule ligand genes are human CD40 ligand genes

30 43. A human cell containing the gene therapy vector of claims 23-36 or 39-42 or the genetic construct of claims 37-38.

44. The human cell of claim 43 wherein said cell is an antigen presenting cell.

45. The human cell of claim 43 wherein said human cell is a neoplastic cell.

46. The human cell of claim 43 wherein said cell is an accessory cell.

5 47. An animal cell containing the gene therapy vector or genetic construct of claims 23-43.

48. An insect cell containing the gene therapy vector or genetic construct of claims 23-43.

10 49. A bacterial cell containing the gene therapy vector or genetic construct of claims 23-43.

50. A method of vaccinating an animal against a predetermined organism comprising: administering into an animal to be immunized against a predetermined organism, a vaccine comprising immunogenic antigens capable of causing 15 an immune response to said predetermined organism together with a vector containing a gene including an accessory molecule ligand.

51. The method of claim 50 wherein said immunogenic antigens are encoded by genes present on a genetic vector.

20 52. The method of claim 50 wherein said gene is a chimeric gene.

53. The method of claim 50 wherein said chimeric gene contains at least a portion of a murine CD40 ligand gene.

25 54. The method of claim 50 wherein said chimeric gene contains at least a segment of a murine CD40 ligand gene and at least a segment of a different accessory molecule gene.

30 55. The method of claim 50 wherein said predetermined organism is a virus, a bacteria, a fungus or a neoplastic cell.

56. A method of producing an immune response directed to a predetermined antigen comprising: administering to said animal a genetic vector containing a gene encoding the

antigen to which said immune response is desired together with a genetic vector containing a gene encoding an accessory molecule ligand gene.

57. A chimeric accessory molecule ligand gene comprising at least one domain or sub-domain gene segment derived from a first accessory molecule ligand gene operatively linked to the domain or sub-domain gene segment of a second accessory molecule ligand gene.

58. The chimeric accessory molecule ligand gene of claim 57 in which said first and second accessory molecule ligand genes are selected from the group consisting of the genes from any species encoding a member of the tumor necrosis family, CD40-ligand, Fas-ligand, CD70, TNF_α, TNF_β, CD30 ligand, 4-1BB ligand (4-1BBL), TNF-related apoptosis inducing ligand (TRAIL) and nerve growth factor.

59. The chimeric accessory molecule ligand gene of claim 57 in which at least one of said domain or sub-domain gene segments is an artificial gene segment.

60. The chimeric accessory molecule encoded by the genes of claims 57-59.

61. A chimeric accessory molecule ligand gene comprising at least a portion of the gene encoding Domains I and II derived from an accessory molecule ligand operatively linked to at least a portion of the gene 25 encoding a Domain of an accessory molecule ligand which in turn is operatively linked to at least a portion of the gene encoding Domain IV of an accessory molecule ligand.

62. The chimeric accessory molecule ligand gene of claim 61 wherein said Domains I and II are derived from the 30 human CD40 ligand gene.

63. The chimeric accessory molecule ligand gene of claim 61 wherein said Domain IV is the human Fas-ligand Domain IV.

64. The chimeric accessory molecule ligand gene of claim 61 wherein said Domain is Domain III of another accessory molecule ligand.

65. The chimeric accessory molecule ligand gene of 5 claim 61 wherein said Domain is a domain from the same accessory molecule ligand.

66. The chimeric accessory molecule ligand gene of claim 61 wherein said Domain is an artificial domain.

67. The method of claim 4 wherein said chimeric gene 10 is a gene of claims 57-60.

68. The method of claim 11 wherein said accessory molecule ligand gene is a chimeric accessory molecule ligand gene of claims 57-60.

69. The gene therapy vector of claim 23 wherein said 15 chimeric gene is a chimeric accessory molecule ligand gene of claims 57-60.

70. A method of treating rheumatoid arthritis in a joint comprising inserting into the joint a vector containing a gene which encodes an accessory molecule 20 ligand so that said accessory molecule ligand is expressed on the surface of cells within the joint.

71. The method of claim 70 wherein said accessory molecule ligand gene is a chimeric accessory molecule ligand gene which is comprised of at least a portion of a 25 human Fas-ligand gene.

72. The method of claim 70 wherein said accessory molecule ligand gene is a chimeric accessory molecule ligand gene which contains at least a portion of the murine Fas-ligand gene.

73. The method of claim 70 wherein said accessory molecule ligand gene is a murine Fas-ligand gene.

74. The method of claim 70 wherein said accessory molecule ligand gene is the murine Fas-ligand gene.

75. The method of claim 70 wherein said accessory molecule ligand gene is a chimeric accessory molecule gene comprised of at least a portion of domain III from the murine Fas-ligand gene and a portion of domain IV from the 5 human Fas-ligand gene.

76. The method of claim 70 wherein said accessory molecule ligand gene is a chimeric accessory molecule ligand gene comprised of a portion of domain III of the human CD70 gene and at least a portion of domain IV of the 10 human Fas-ligand gene.

77. A method of treating rheumatoid arthritis in a joint comprising inserting into the joint cells which have been transformed with a gene which encodes an accessory molecule ligand which is expressed on the surface of said 15 cells.

78. A chimeric accessory molecule ligand comprised of at least a portion of the fourth domain of human Fas-ligand.

79. A chimeric accessory molecule ligand derived from 20 a Fas-ligand in which at least one matrix metalloproteinase cleavage site has been removed.

80. A chimeric accessory molecule ligand comprised of domain III of the Murine Fas-ligand or the human CD70 gene, and domain IV of the human Fas-ligand.

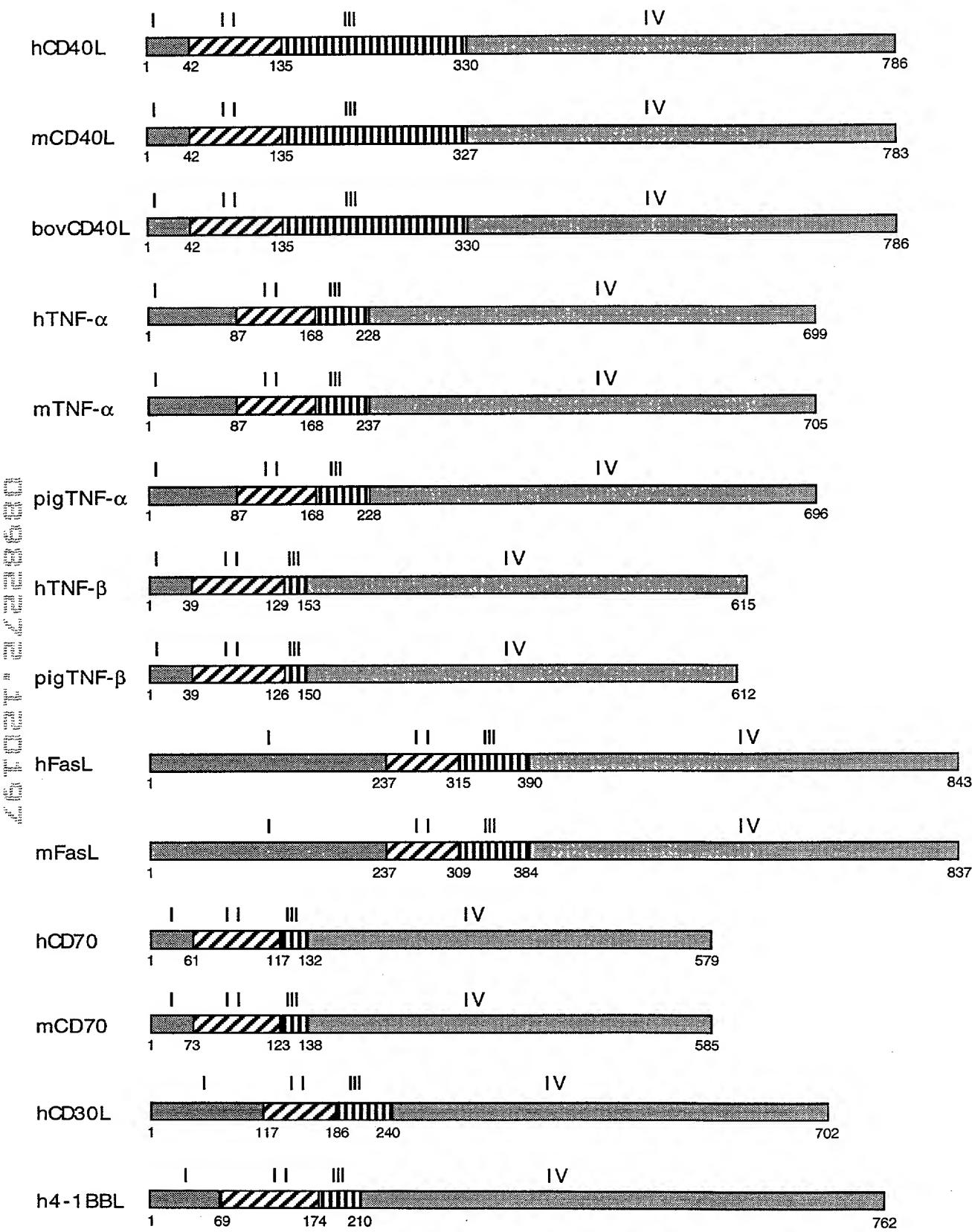
81. A gene therapy vector containing a gene encoding 25 chimeric accessory molecule of claims 78-80.

82. A cell containing a gene therapy vector of claim 81.

83. A method of altering the immunoreactivity of 30 human cells, which method comprising introducing a gene encoding an accessory molecule ligand which has a stabilized activity into said cells so that said accessory molecule ligand is expressed on the surface of said cells.

ABSTRACT

This invention relates to genes which encode accessory molecule ligands and their use for immunomodulation, 5 vaccination and treatments of various human diseases, including malignancies and autoimmune diseases. This invention also describes the use of accessory molecule ligands which are made up of various domains and subdomain portions of molecules derived from the tumor necrosis 10 factor family. The chimeric molecules of this invention contain unique properties which lead to the stabilization of their activities and thus greater usefulness in the treatment of diseases. Vectors for expressing genes which encode the accessory molecule ligands of this invention are 15 also disclosed.



DOMAINS: I - Cytoplasmic Domain; II - Transmembrane Domain; III - Proximal Extracellular Domain; IV - Distal Extracellular Domain (putative soluble form)

Figure 1

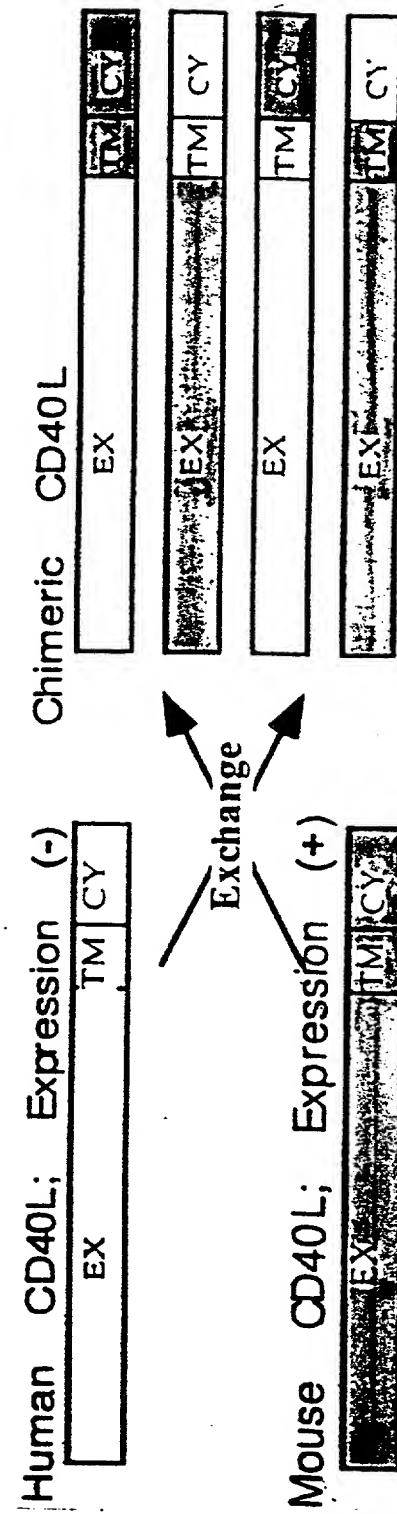


Figure 2

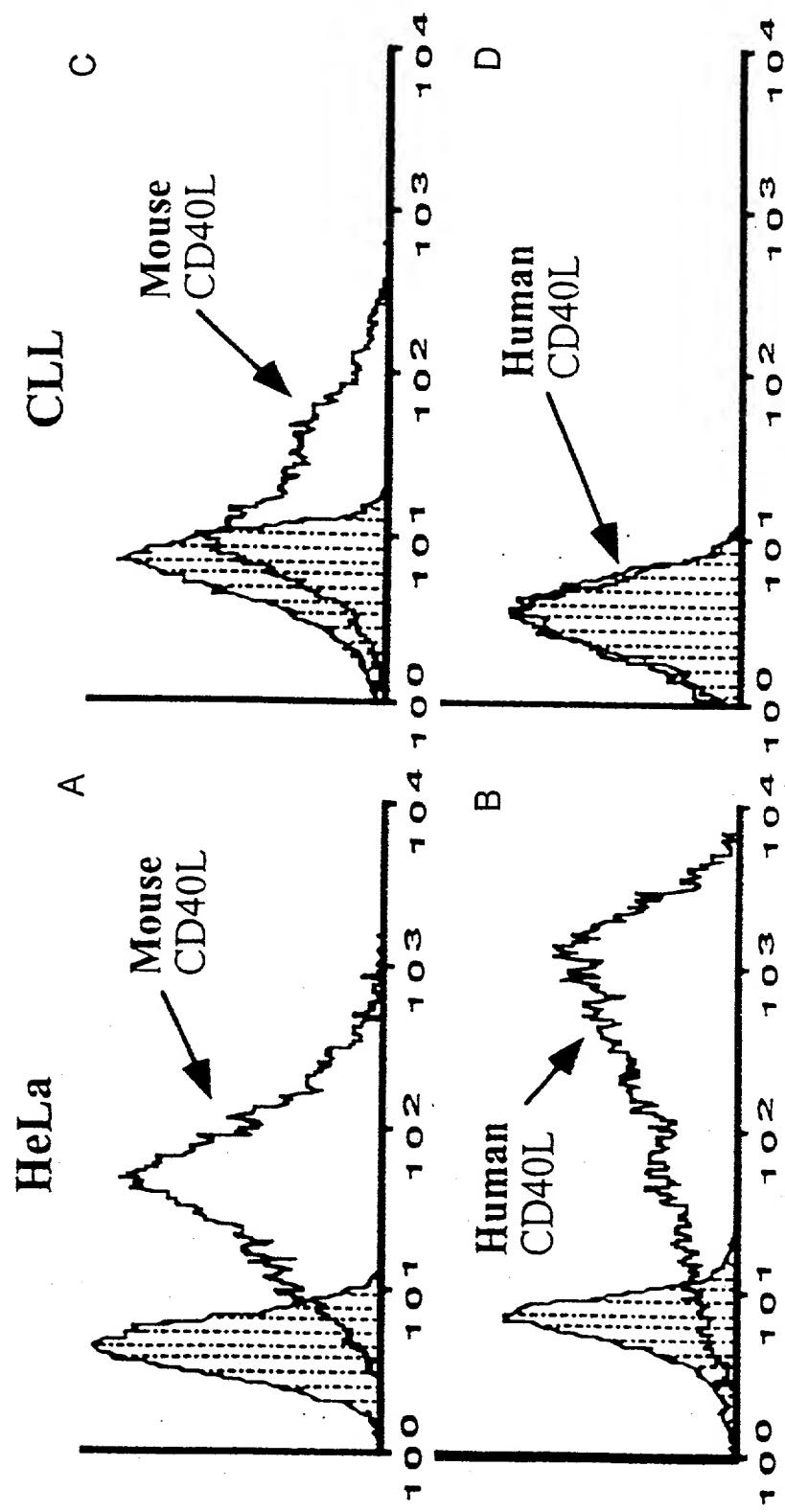


Figure 3

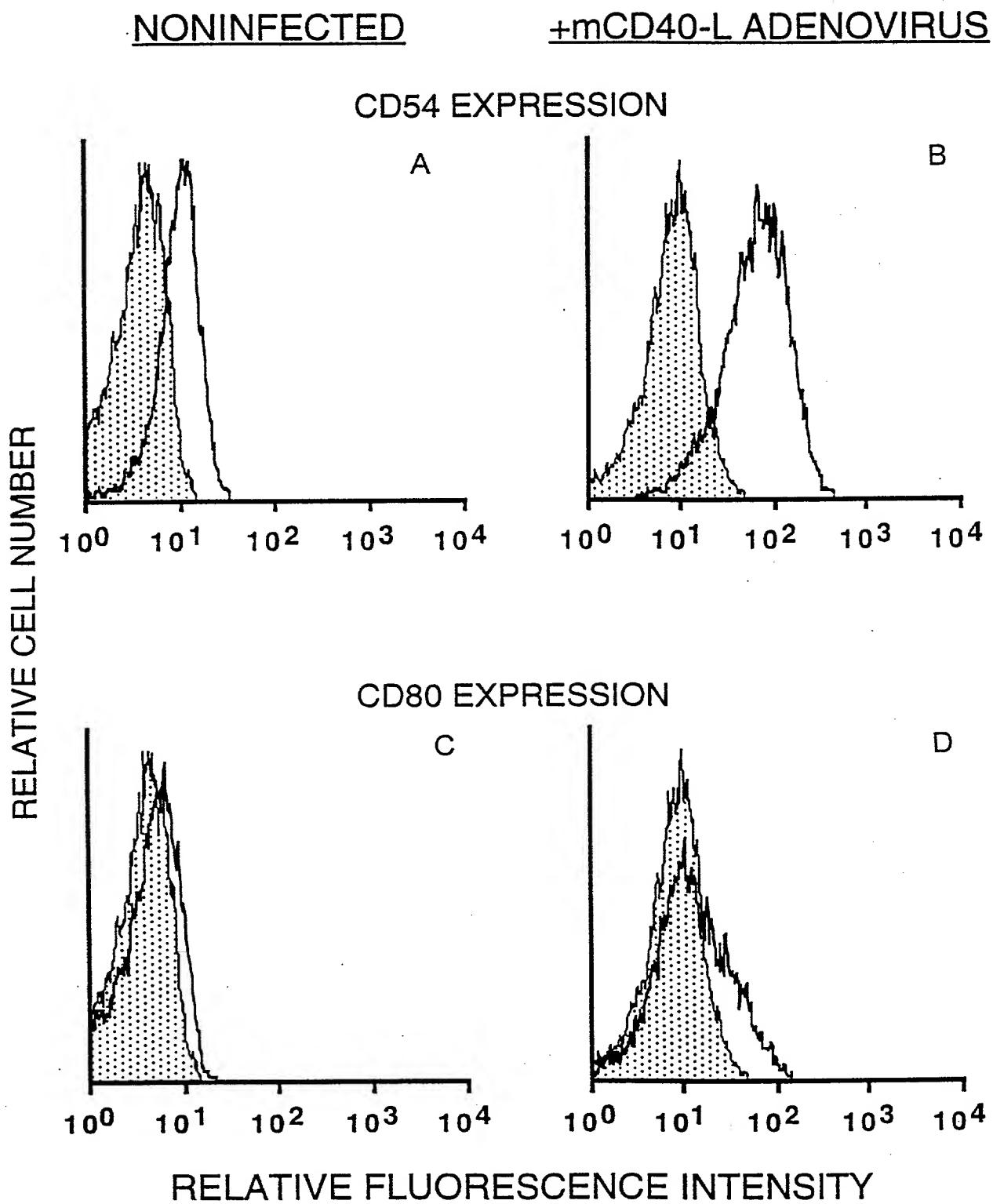


Figure 4

Allogenic T cell response to CLL cells transfected with adeno-mCD40L

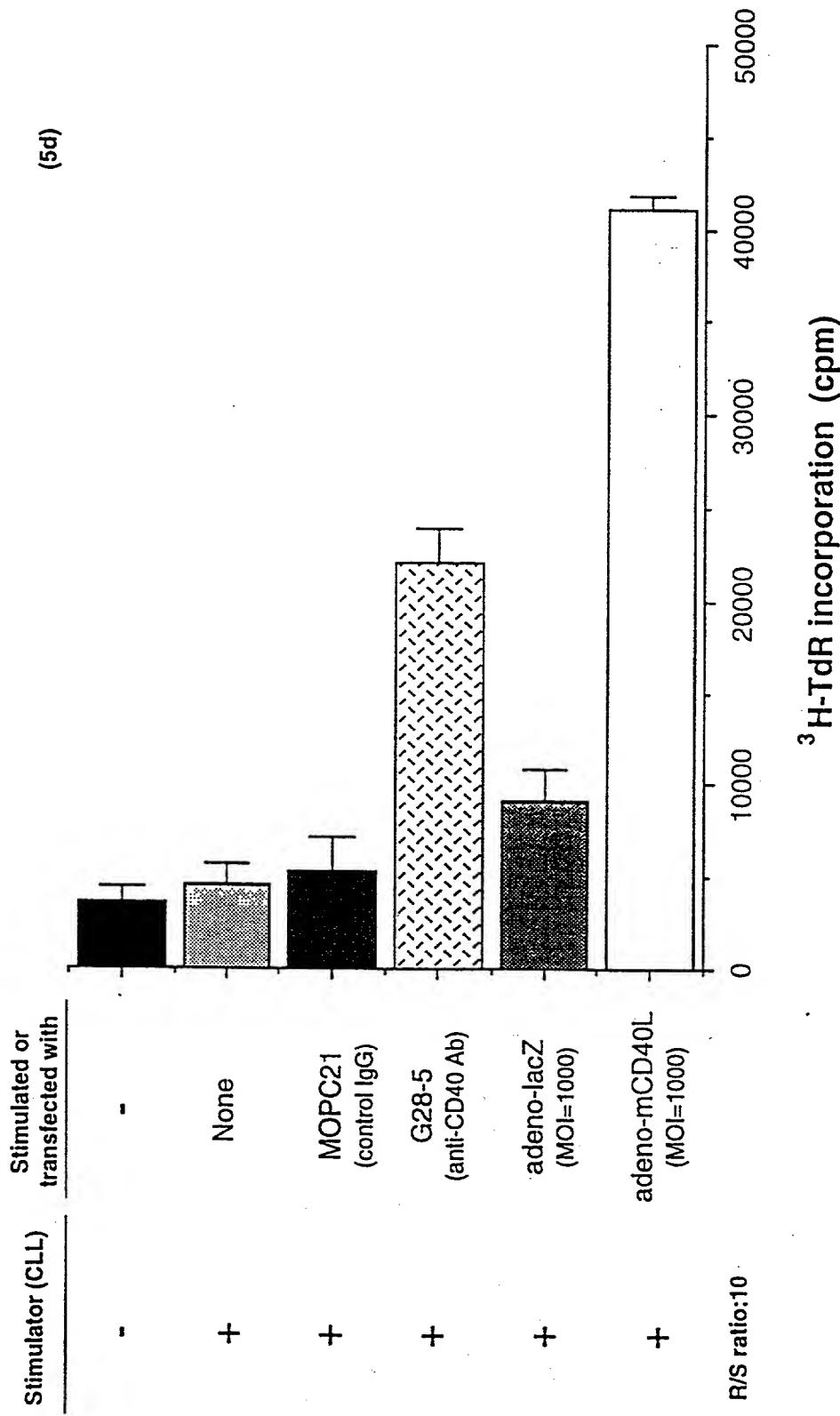


Figure 5

Production of IFN γ by allogenic T lymphocytes stimulated with CLL B cells

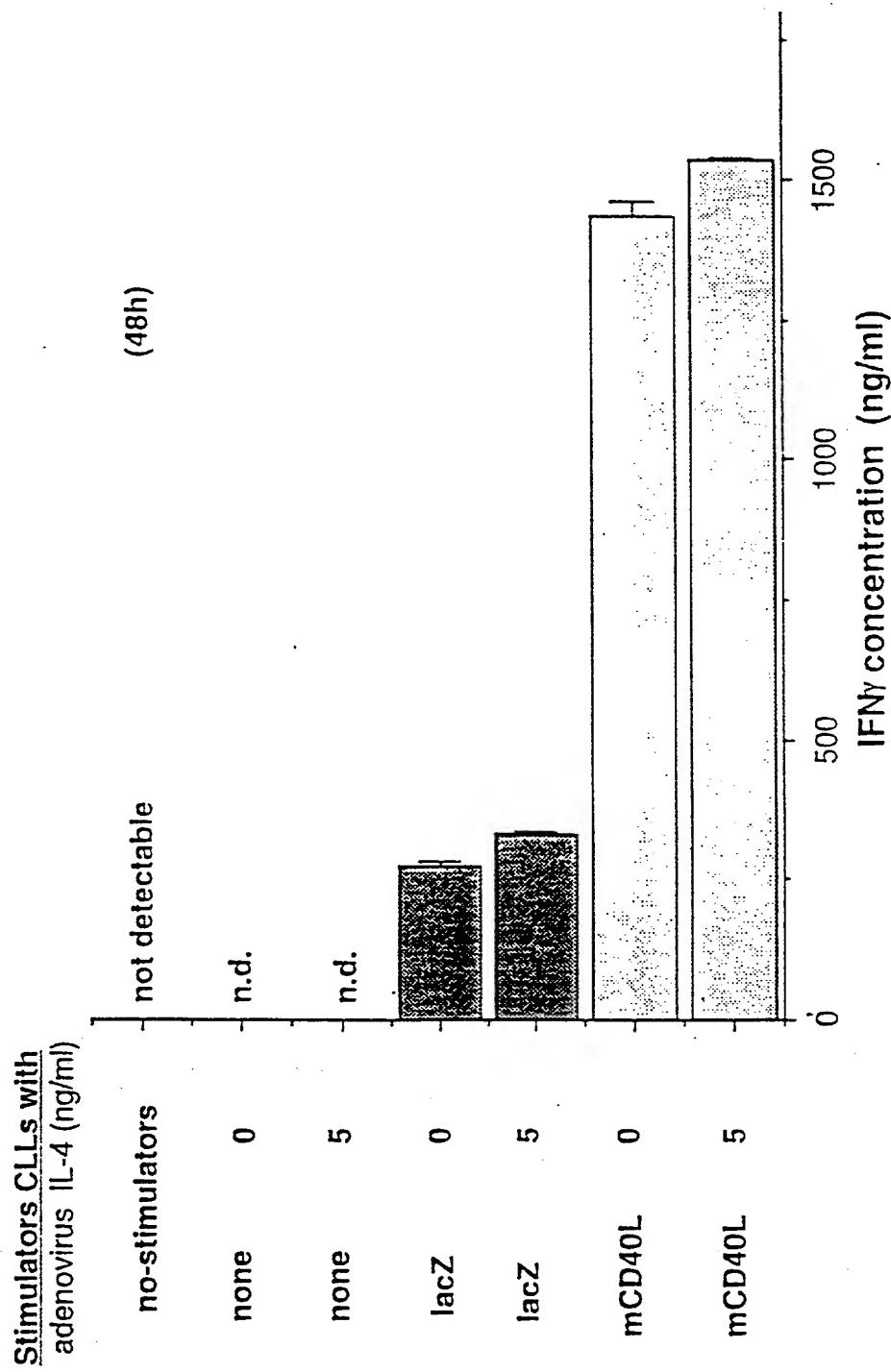


Figure 6

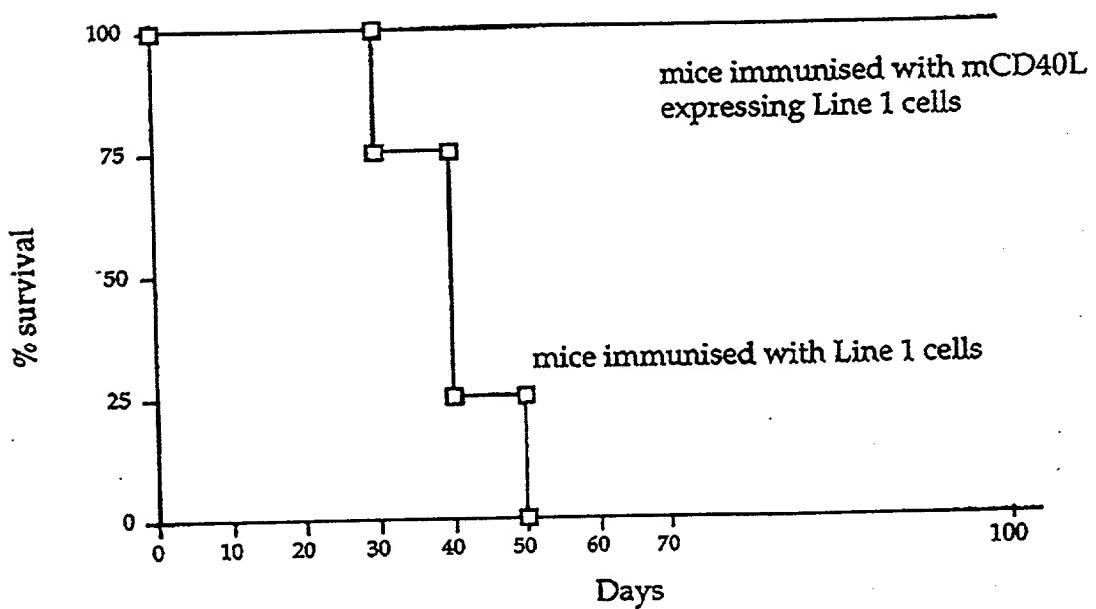


Figure 7

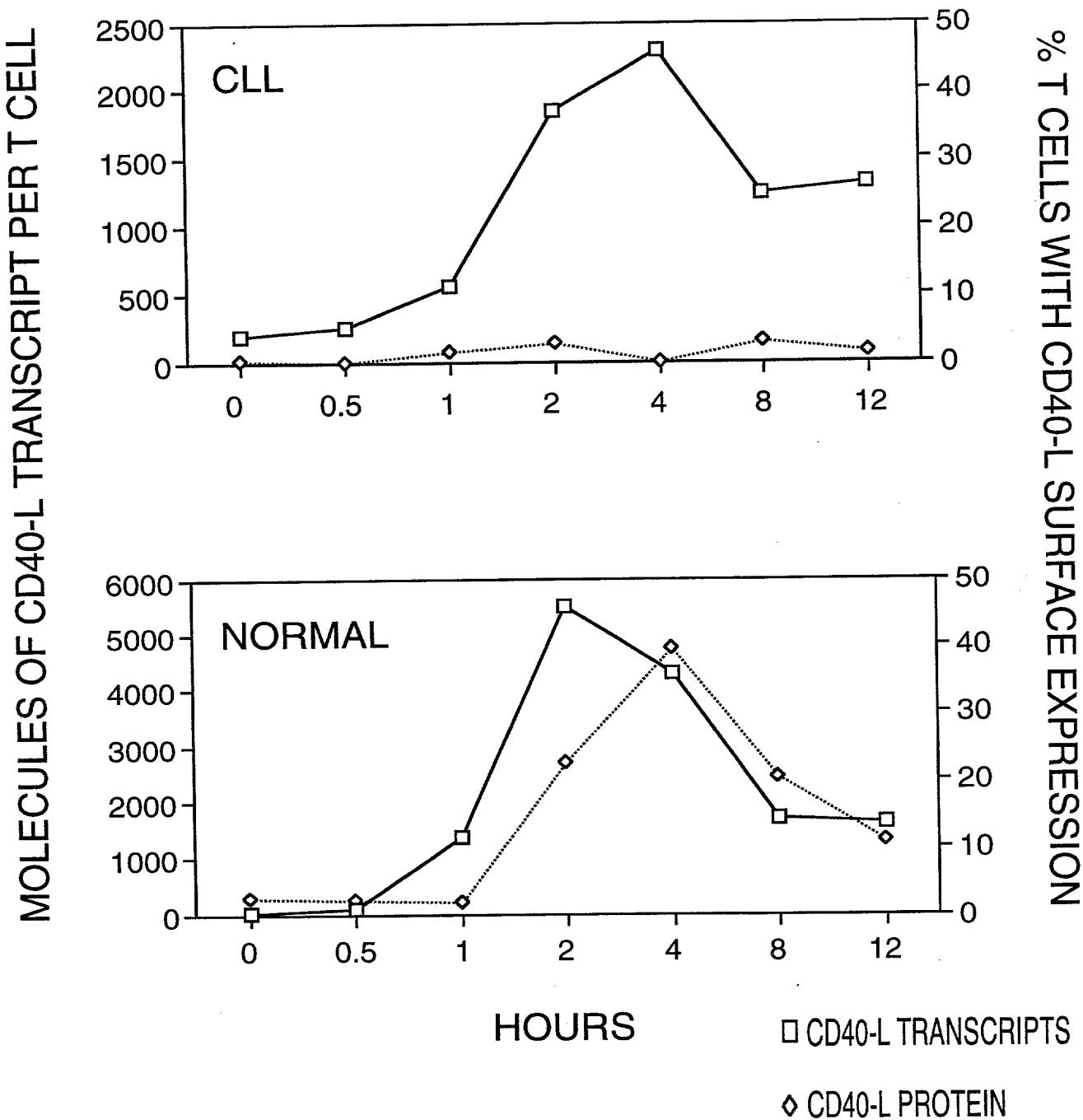


Figure 8

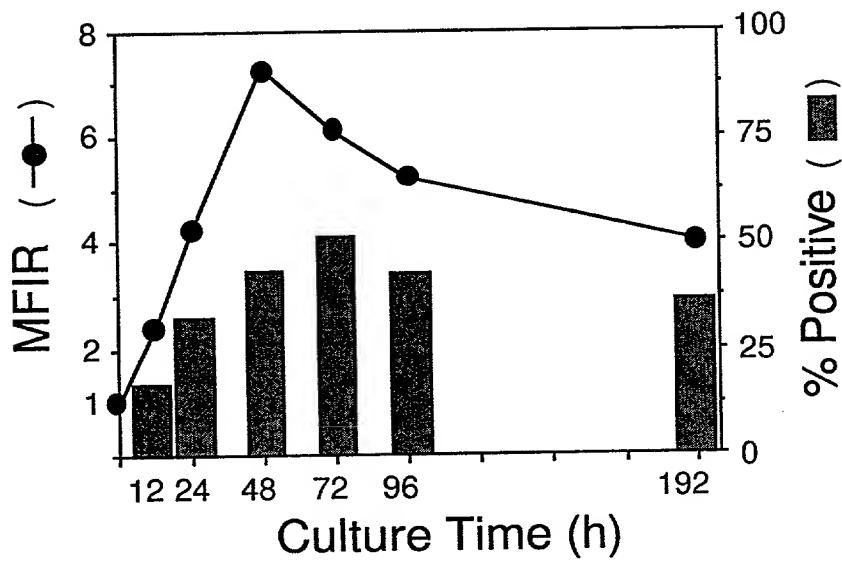


Figure 9

Green Fluorescence Intensity

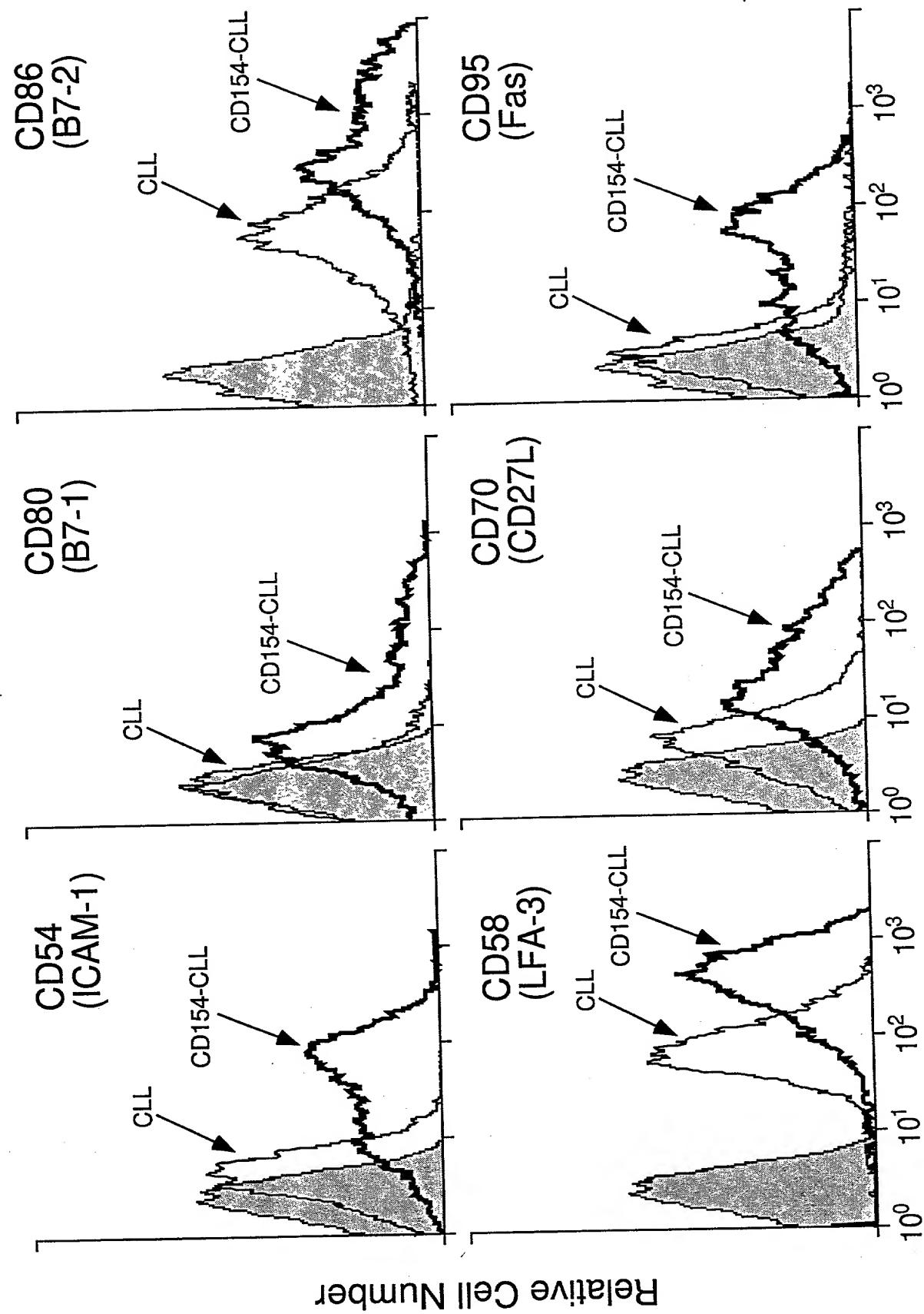
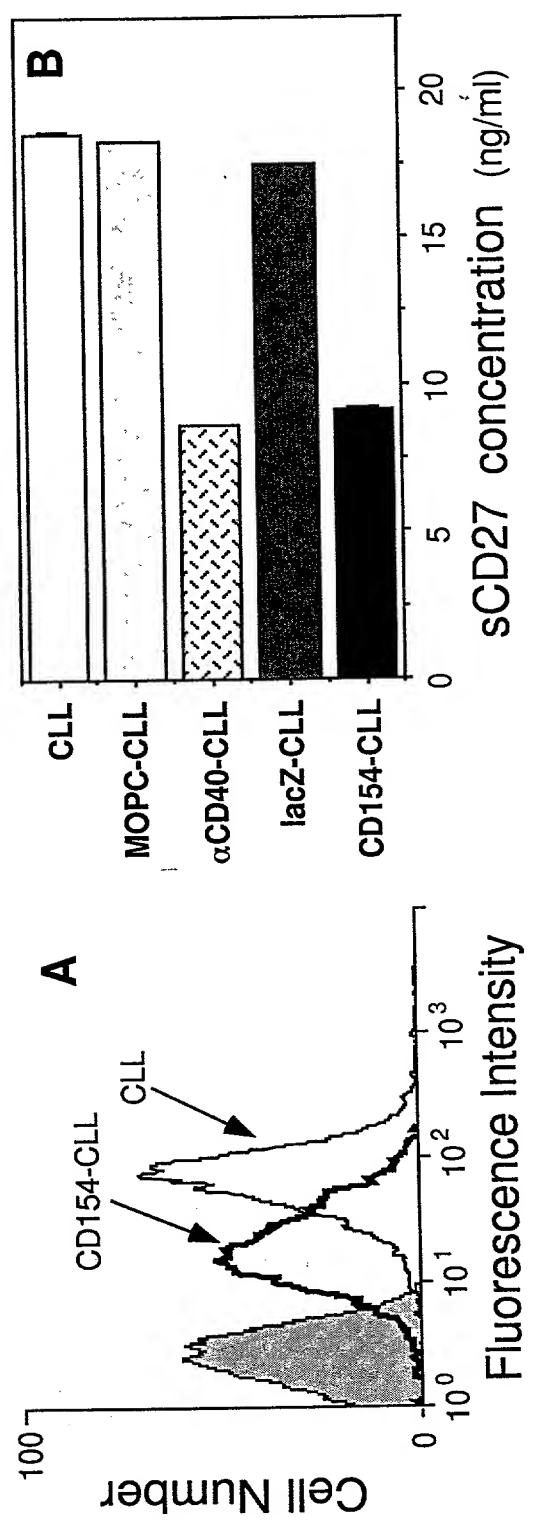


Figure 10

Figure 11



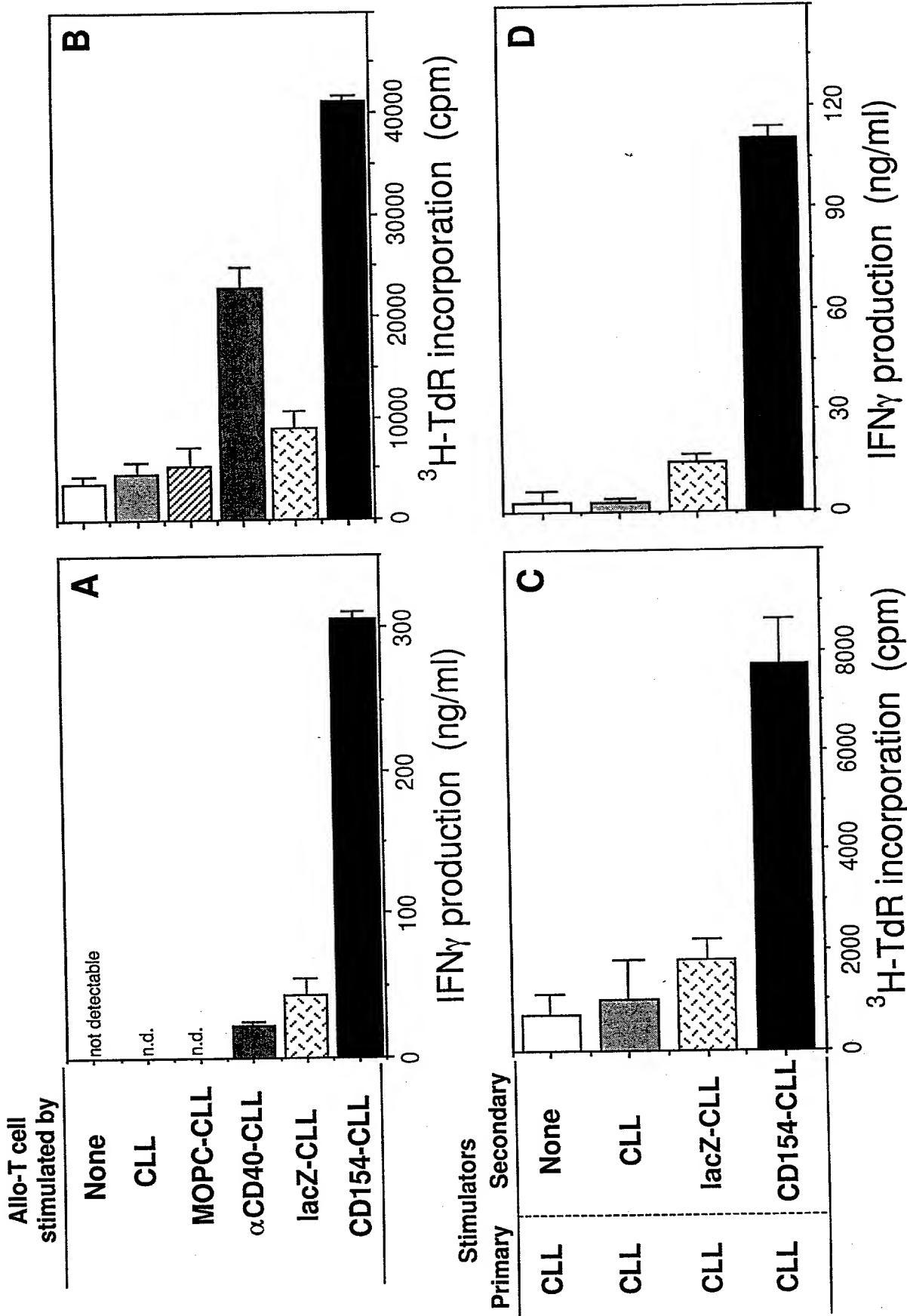
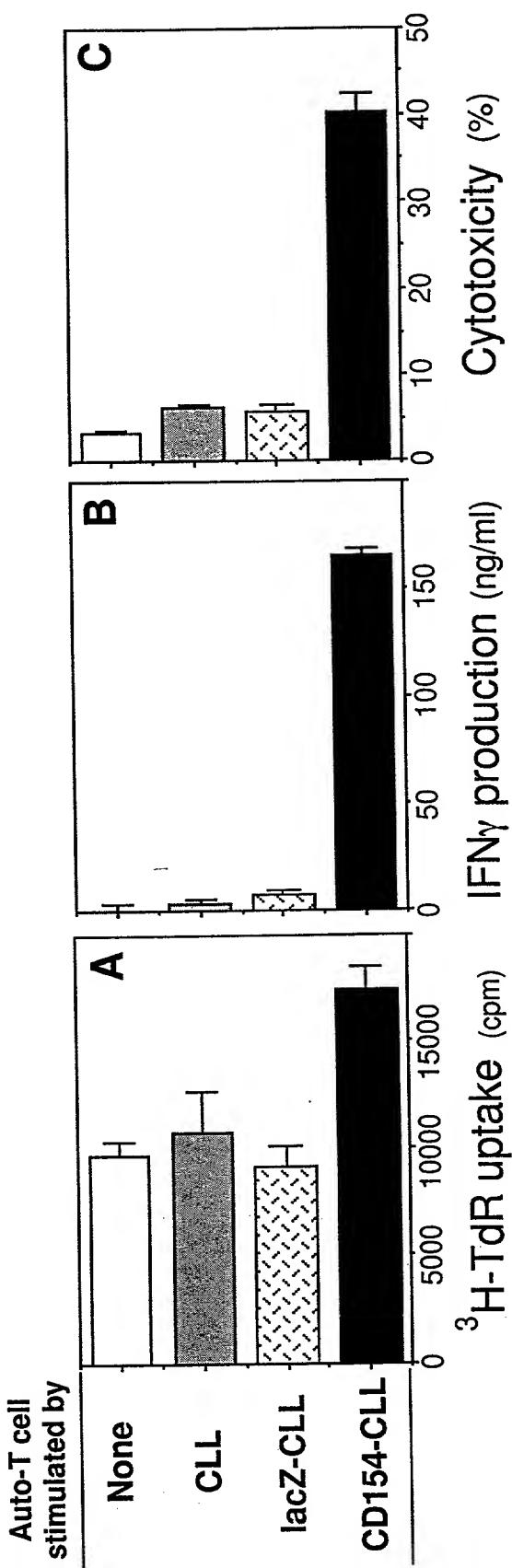


Figure 12

Figure 13



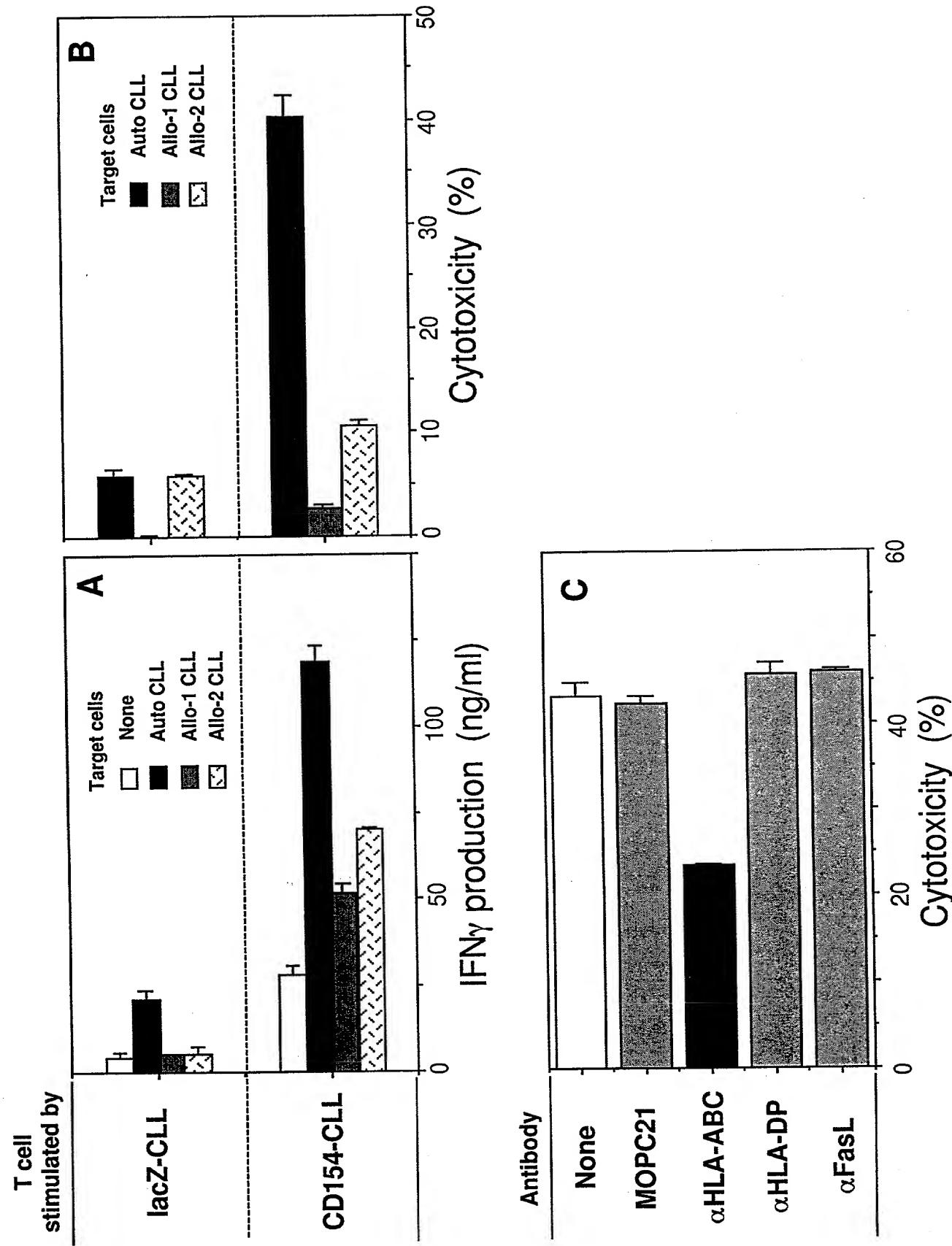


Figure 14

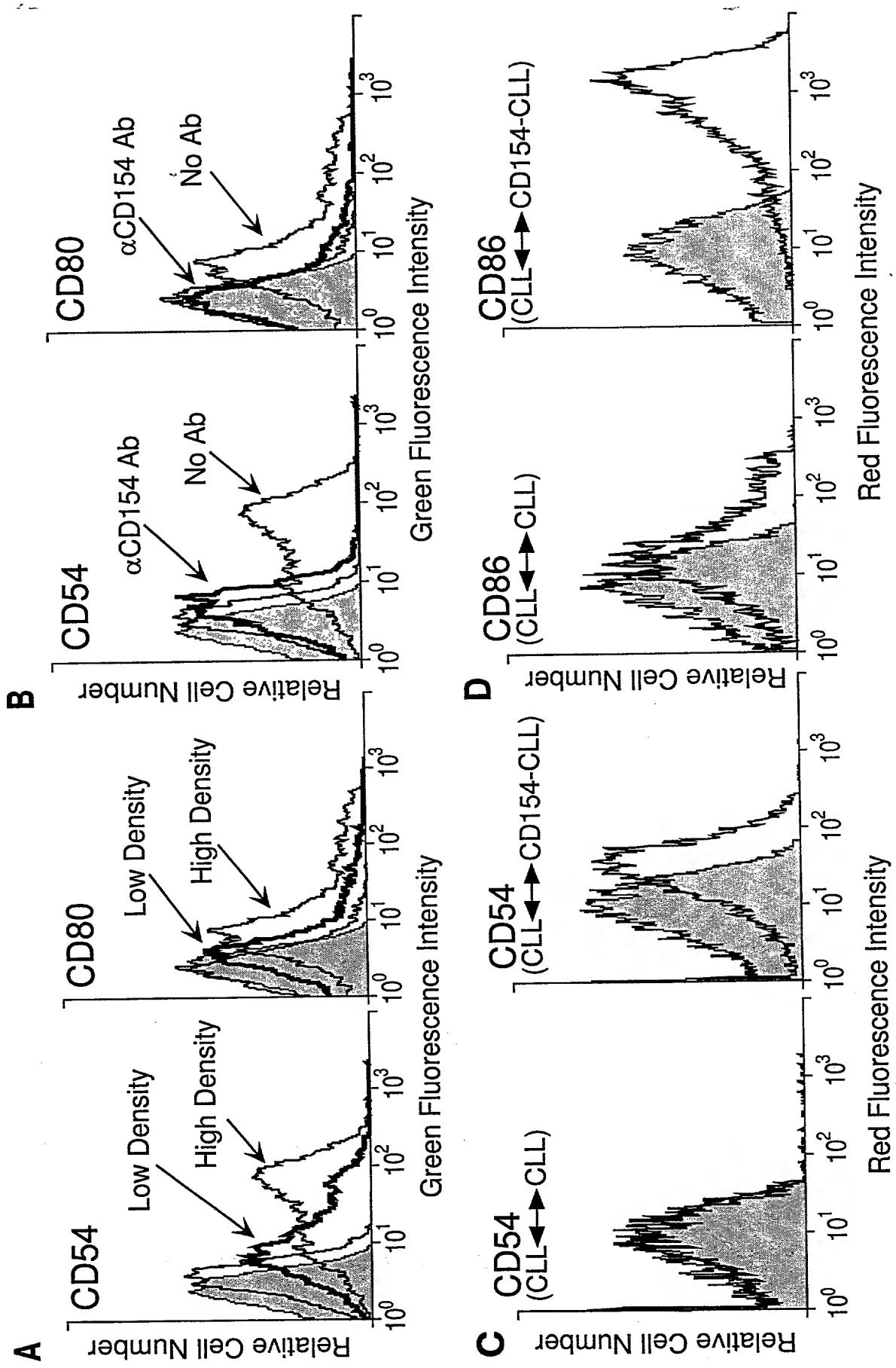


Figure 15

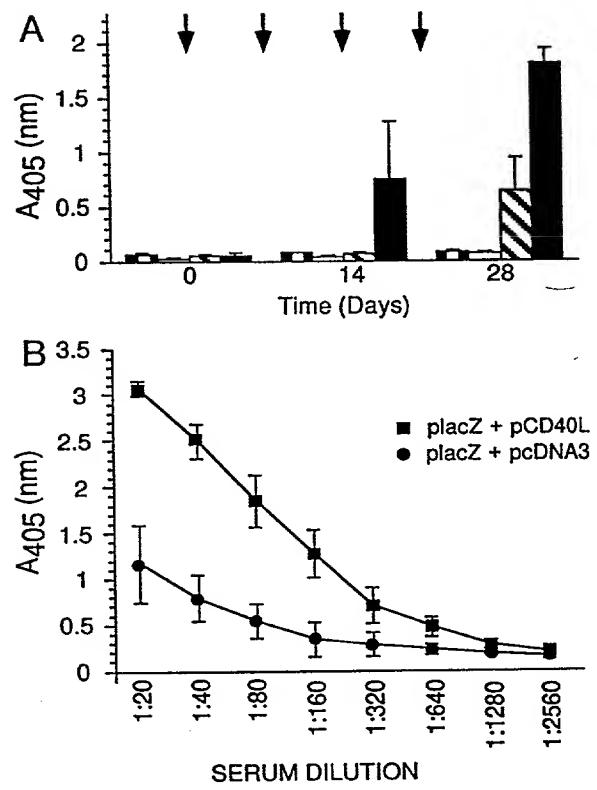


Figure 16

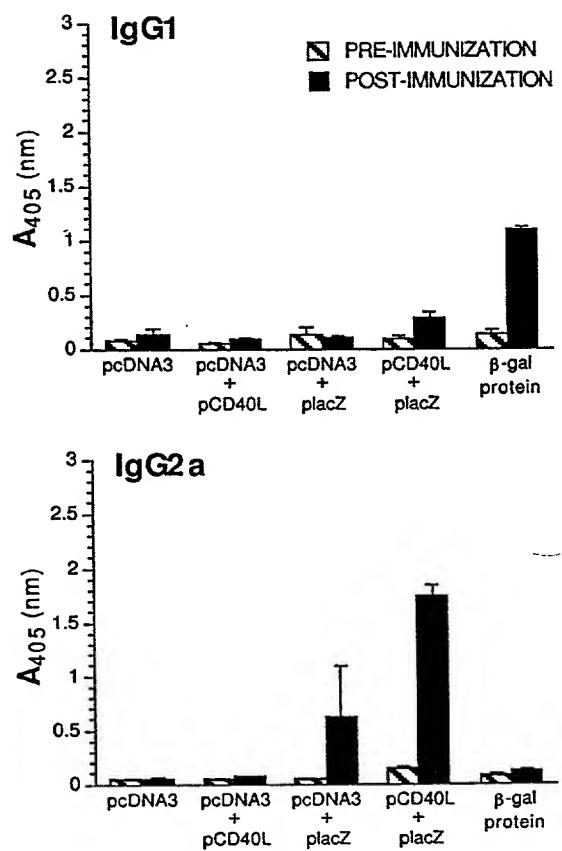


Figure 17

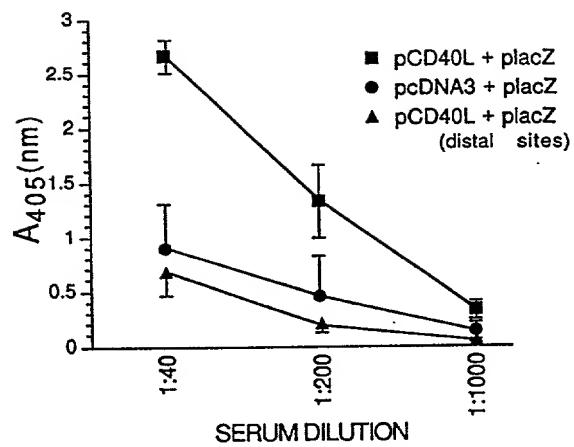


Figure 18

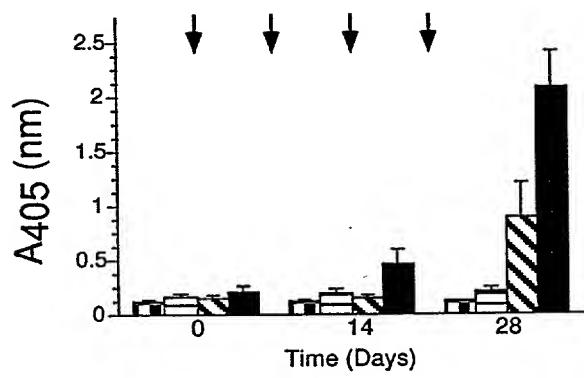


Figure 19

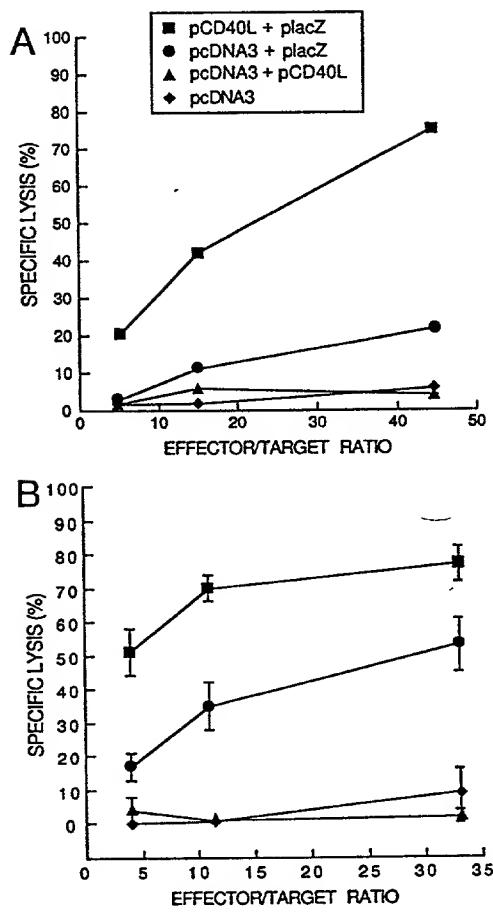
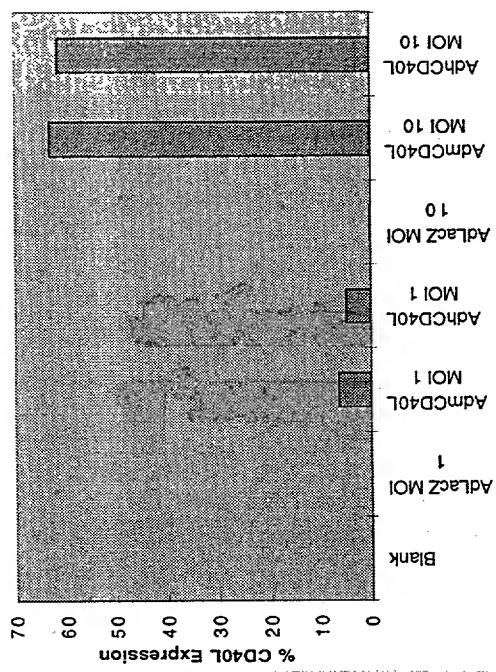


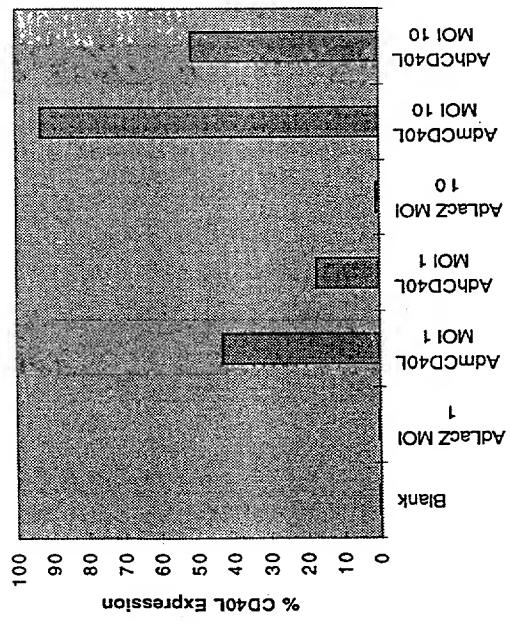
Figure 20

Figure 21

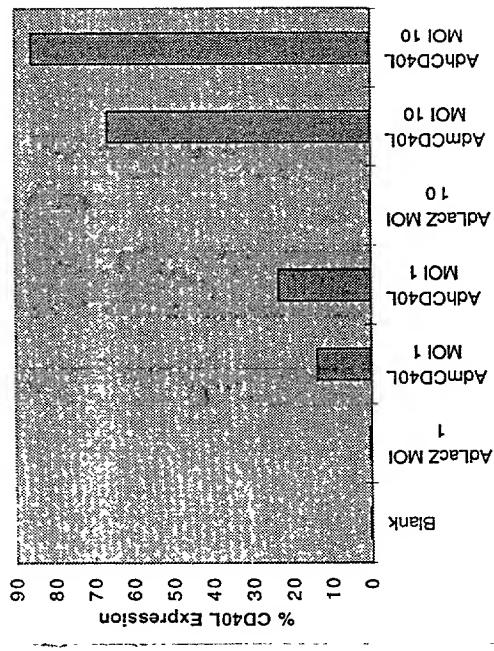
A HeLa Cells



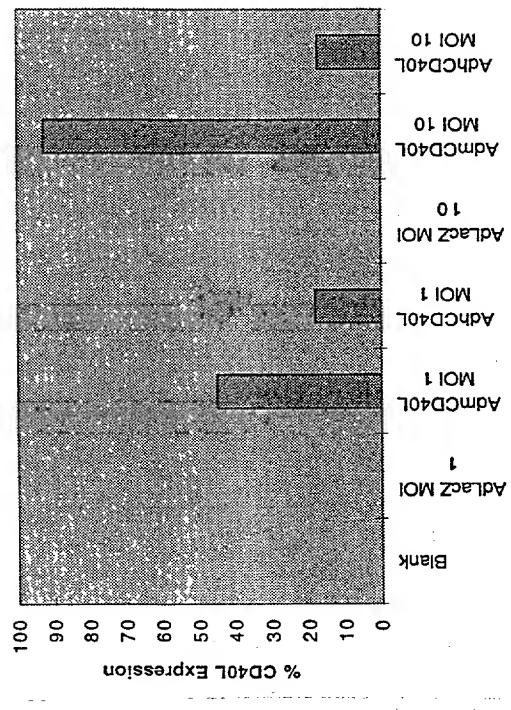
C, NCI 460 Large Cell CA (CD40+)



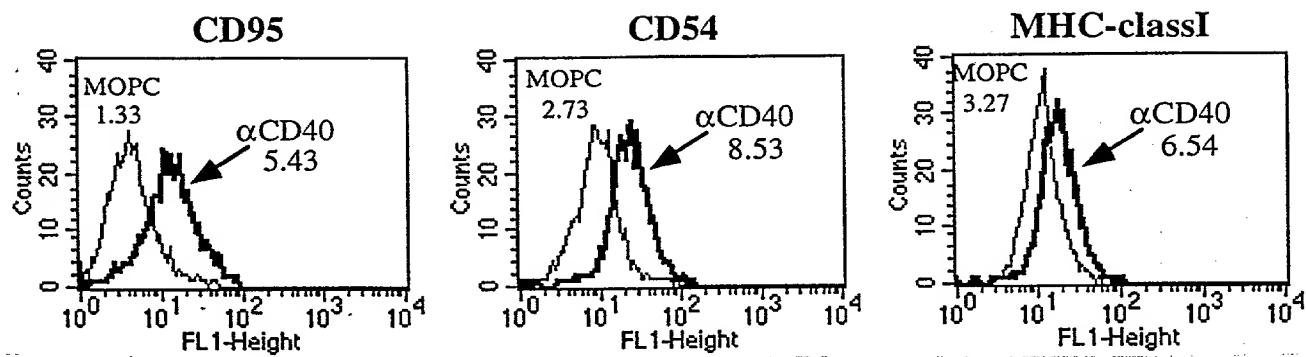
B A427 Lung CA (CD40-)



D SK-Mes-1 Squamous Cell (CD40++)



A



B

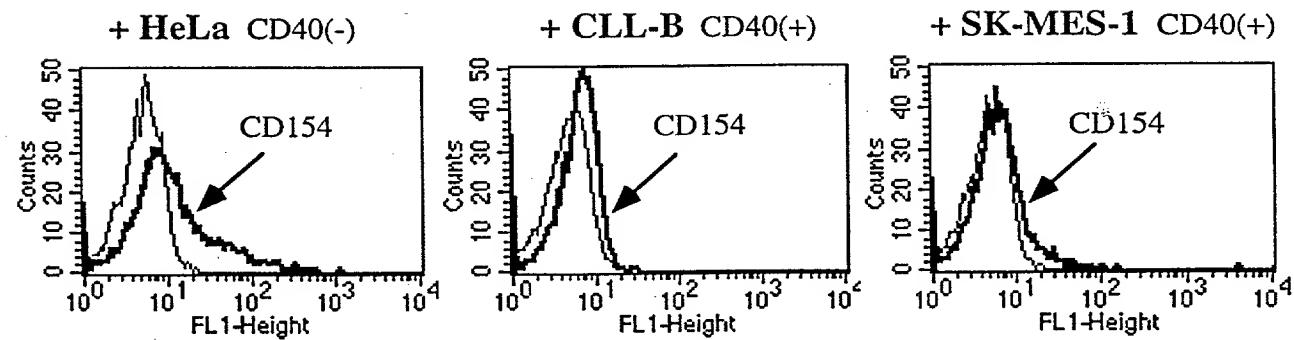


Figure 22

RA SYNOVIAL FLUID AND PLASMA INHIBITION OF FAS-LIGAND

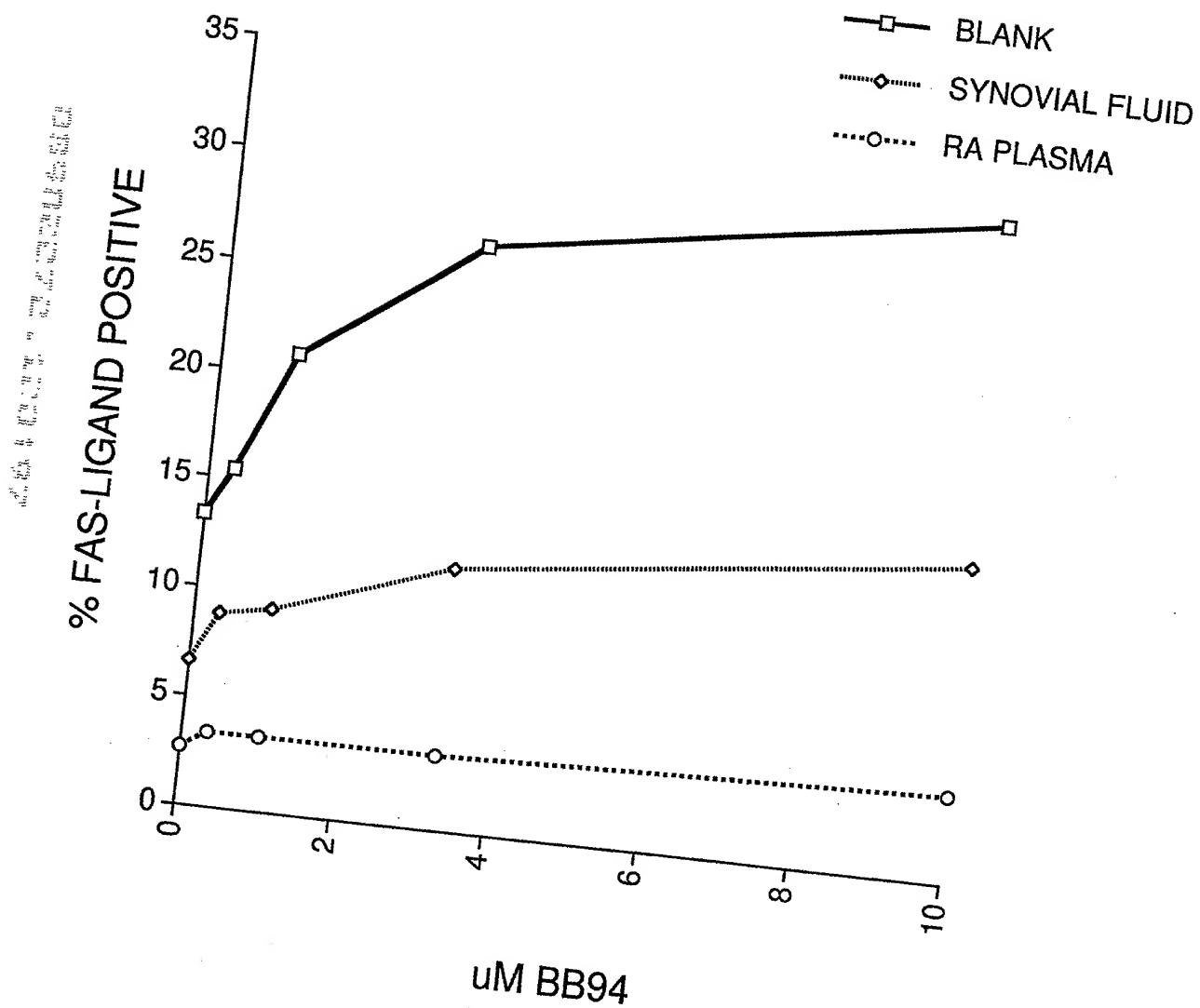


Figure 23

Gene Therapy of Leukemia

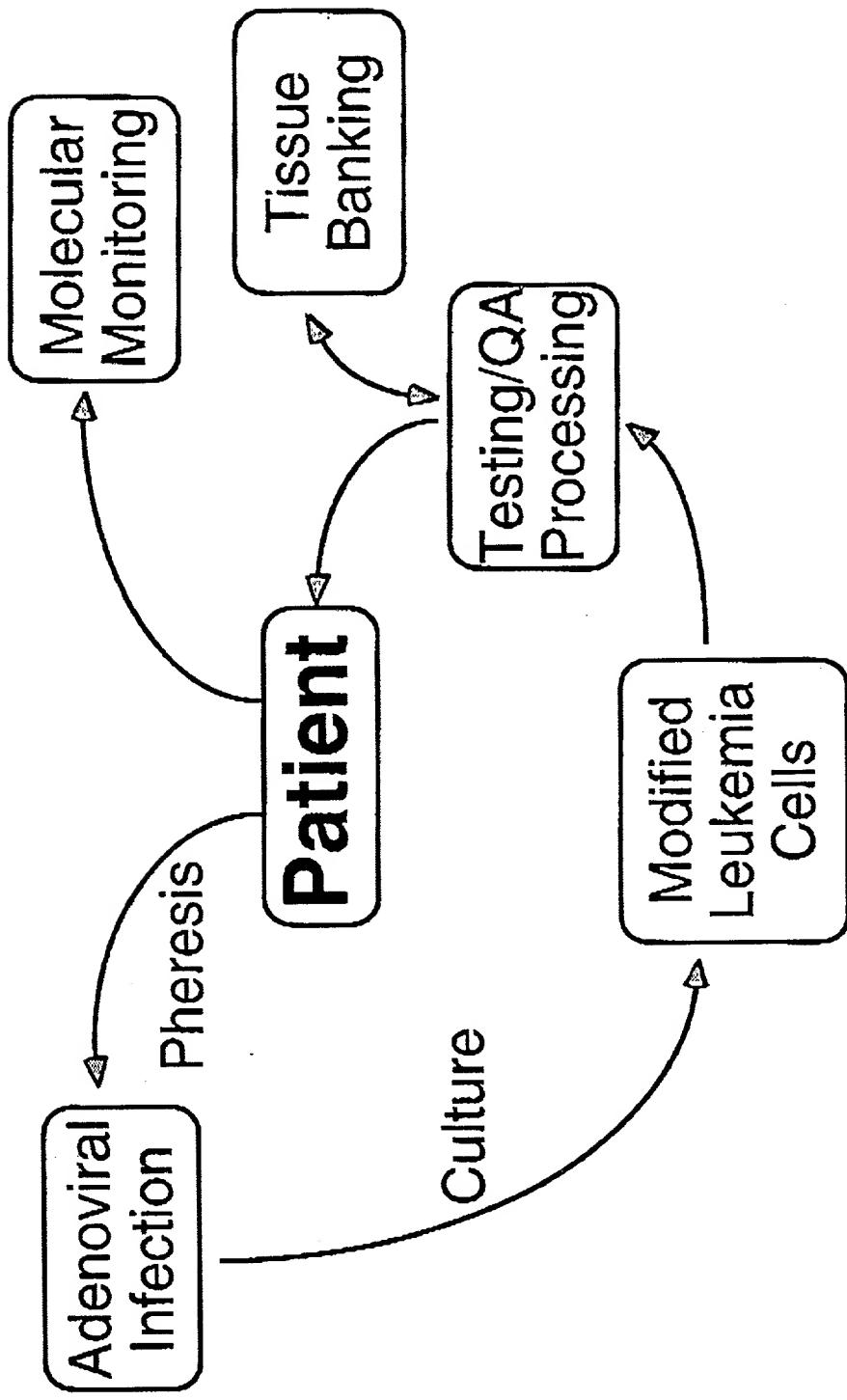


Figure 24

1 MOOPFNYPYPOIYWVDSSASSPWAPPGTVPCTSVPRRGQRRPPPPP 50
1 MQQPFNYPYPOIYWVDSSASSPWAPPGTVPCTSVPRRGQRRPPPPP 50
51 PPPLPPPPPPPLPPLPLKKGHNHSTGLCLLMFFMVLVALVGLGLG 100
51 PPPLPPPPPPPLPPLPLKKGHNHSTGLCLLMFFMVLVALVGLGLG 100
101 MFQLFHLOKELAELRESTSQMHTASSLEKQIGHPSPPPEKKELRKVAHLT 150
101 MFQLFHLOKELAELREFTNQSLKVSSFEKQIGHPSPPPEKKELRKVAHLT 150
151 GKSNSRSMPLEWEDTYGIVLLSGVKYKKGGLVINETGLYFVYSKVYFRGQ 200
151 GKSNSRSMPLEWEDTYGIVLLSGVKYKKGGLVINETGLYFVYSKVYFRGQ 200
201 SCNNLPLSHKVYMRNSKYPQDLVMMEGKMMSYCTTGQMWARSSYLGAVFN 250
201 SCNNLPLSHKVYMRNSKYPQDLVMMEGKMMSYCTTGQMWARSSYLGAVFN 250
251 LTSADHLYVNSELSLVNFEESQTFFGLYKL 281
251 LTSADHLYVNSELSLVNFEESQTFFGLYKL 281

Figure 25

08952523214265497
1 MQQPFNYPYPOIYWVDSSASSPWAPPGVLPCTSPRRPGQRRPPPPP 50
1 MQQPFNYPYPOIYWVDSSASSPWAPPGVLPCTSPRRPGQRRPPPPP 50
51 PPPLPPPPPPPLPPLPLPPLKKRGNHSTGLCLLVMFFMVLVALVGLGLG 100
51 PPPLPPPPPPPLPPLPLPPLKKRGNHSTGLCLLVMFFMVLVALVGLGLG 100
101 MFQLFHILEALRESTSMHTASSLEKOIGHPSPPEKKELRKVAHIT 150
101 MFQLFR.....:.....FAQAIGHPSPPEKKELRKVAHIT 130
151 GKSNSRSMPLEWEDTYGIVLLSGVKYKKGLVINETGLYFVYSKVFRCQ 200
131 GKSNSRSMPLEWEDTYGIVLLSGVKYKKGLVINETGLYFVYSKVFRCQ 180
201 SCNLPLSHKVYMRNSKYPQDLVMMEGKMMSYCTTGQMWARSSYLGAVFN 250
181 SCNLPLSHKVYMRNSKYPQDLVMMEGKMMSYCTTGQMWARSSYLGAVFN 230
251 LTSADHLYVNSELSLVNFEESQTFFGLYKL 281
231 LTSADHLYVNSELSLVNFEESQTFFGLYKL 261

Figure 26

1 MOOPFNYPYPQIYWVDSSASSFWAPPGTVLPCPTSVPRPGQRRPPPPP 50
1 MQQPENYPPQIYWVDSSASSFWAPPGTVLPCPTSVPRPGQRRPPPPP 50
51 PPPLPPPPPPPPPLPPLPLPPLKKRGNHSTGLCLLVMF FMVLVALVGLGLG 100
51 PPPLPPPPPPPPPLPPLPLPPLKKRGNHSTGLCLLVMF FMVLVALVGLGLG 100
101 MFQLFHLOKELAELRESTSOMHTASSLEKQQIGHPSPPPEKELRKVAHLT 150
101 MFQLF.....MPEEGSGCSVRRPYGCVLRIGHPSPPPEKELRKVAHLT 145
151 GKSNSRSMPLEWEDTYGIVLLSGVKYKKGGLVINETGLYFVYSKVYFRQ 200
146 GKSNSRSMPLEWEDTYGIVLLSGVKYKKGGLVINETGLYFVYSKVYFRQ 195
201 SCNNLPLSHKVYMRNSKYPODLVMMEGKMMSYCTTGQMWARSSYLGA FN 250
196 SCNNLPLSHKVYMRNSKYPODLVMMEGKMMSYCTTGQMWARSSYLGA FN 245
251 LTSADHLYVNSELSLVNFEESQTFFGLYKL 281
246 LTSADHLYVNSELSLVNFEESQTFFGLYKL 276

Figure 27

Matrix Metalloproteinase Cleavage Sites

	P_4	P_3	P_2	P_1	P'_1	P'_2	P'_3	P'_4
Cleavage								
\Downarrow								
Collagenases								
MMP-1								
P_4	Ala	Pro	Leu	Gly	Met	Arg	Met/Ala	Arg
Gly/Leu				His	Leu	Leu	Gly	Lys
Met	Ala	Asp	Val/Gly	Glu	Ile	Phe	Val	Gln
Glu			Ile	Tyr	Gln	Trp	Ser	Ile
Pro	Ser	Gln/Arg	Ala	Ala	Pro	Glu	Glu	Gly
Tyr	Glu	Asp	Phe	Phe	Phe	Pro	Phe	Ser
Ile	Gly	Glu	Gln	Ala	Ala	Arg	Arg	Glu
Thr	Arg	Ala	Asn	Tyr/Val	Val/Gly	Pro	Pro	Ala
				[not K,E,W]	Ser			
MMP-8								
P_4	Ala	Pro	Leu	Glu	Tyr	Ala	Gly	Arg
Gly/Leu				Ala	Ile	Leu	Met	Gln
Met					Leu	Val	Ala	
Glu						Trp		
Pro								
Tyr/Ile/Thr/Arg (otherwise same as MMP-1)								

Figure 28A

Gelatinases

P_4 P_3 P_2 P'_1 P'_2 P'_3 P'_4

MMP-2	Gelatinase A	P_4	P_3	P_2	P_1	P'_1	P'_2	P'_3	P'_4
		Gly	Pro	Arg	Gly	Leu	Ala/Leu	Gly/Ala	Gln
		Ile	Ala	Gln	Asn	Ile/Phe	Phe/Trp	Leu	Arg
		Pro	Arg	Leu	Ala	Val/Met	Gly	Ser	His
		Arg		Ala	His	Ala	Arg/Gln	Pro	Pro
		Leu		Lys	Leu	Glu	His		
				Ile	Tyr	Gln/Asn			
						Ser	Val		

Gelatinase B

P_4 P_3 P_2 P'_1 P'_2 P'_3 P'_4

MMP-9	Gelatinase B	P_4	P_3	P_2	P_1	P'_1	P'_2	P'_3	P'_4
		Gln/Arg	Pro	Arg	Gly	Ile/Phe	Ala/Leu/Phe	Ala	Thr
						Val/Met	Trp/Gly	Ser	
						Ala		Gly	

Stromelysins

MMP-3	Stromelysin 1	P_4	P_3	P_2	P_1	P'_1	P'_2	P'_3	P'_4
		Asp	Pro	Phe	Glu	Leu	Arg	Ala	Thr
		Gly	Ala	Leu/Met	Ala	Phen	Leu/Phe	Arg/Met	
		Gln/Arg							
		Leu	Val	Tyr	Gln/Phe	Trp/Tyr	Trp	Gly	
		Ile	Leu	Pro/Gly/Glu	Asn	Ile	Val	Val/Ile	
		Glu/Val							
		Leu	Thr	Ile	His	Val	Gln	Ser/Asn	
		Lys	Phe	Ala	Gly	Met	His/Met	Glu/Thr	
		Gly/Asp							
		Arg	Arg	Ser		Leu/Pro	Glu	Ser/Thr	
		Ser/Lys/Phe							
		Pro/Met							
		Ala/Phe/Gln							
									Lys/Tyr/Arg

Figure 28B

MMP-10	Stromelysin 2	P₁ His Leu	P'₁ Ile Leu	P'₂ Gln Val	P'₃ Ala Glu
		P₂ Ile			
		Ala			
		Pro			
Others					
MMP-7	Matrilysin	P'₁ Leu Ile Met	P'₂ Arg Met	P'₃ Ala Gly	P'₄ Gln
		Pro	Gln	Val	
		Leu			
Others					
MMP-7	Matrilysin	P₁ Glu Met/Ala Pro/Gln Gly	P₂ Leu Gln Val	P'₁ Leu Ile Met	P'₂ Arg Met
		Pro			
		Leu			

Figure 28C

PAGE: 1

**RAW SEQUENCE LISTING
PATENT APPLICATION US/08/982,272**DATE: 01/14/98
TIME: 16:27:27**INPUT SET: S22605.raw**

This Raw Listing contains the General
Information Section and up to the first 5 pages.

SEQUENCE LISTING**1 (1) General Information:****2 (1) APPLICANTS:**
3 Kipps, Thomas J.
4 Sharma, Sanjai
5 Cantwell, Mark**6 (ii) TITLE OF INVENTION:** NOVEL EXPRESSION VECTORS
7 CONTAINING ACCESSORY
8 MOLECULE LIGAND GENES AND
9 THEIR USE FOR IMMUNO-
10 MODULATION AND TREATMENT OF
11 MALIGNANCIES**12 (iii) NUMBER OF SEQUENCES:** 44**13 (iv) CORRESPONDENCE ADDRESS:****14 (A) ADDRESSEE:** Lyon & Lyon
15 (B) STREET: 633 West Fifth Street
16 (C) CITY: Suite 4700
17 (D) STATE: Los Angeles
18 (E) COUNTRY: California
19 (F) ZIP: U.S.A.
20 (F) ZIP: 90071-2066**21 (v) COMPUTER READABLE FORM:****22 (A) MEDIUM TYPE:** 3.5" Diskette,
23 (C) OPERATING SYSTEM: IBM P.C. DOS 5.0
24 (B) COMPUTER: IBM Compatible
25 (D) SOFTWARE: FastSeq Version 2.0**26 (vi) CURRENT APPLICATION DATA:****27 (A) APPLICATION NUMBER:** To Be Assigned
28 (B) FILING DATE:--> 45
46*ENTERED*

RAW SEQUENCE LISTING
PATENT APPLICATION US/08/982,272DATE: 01/14/98
TIME: 16:27:31

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47 (C) CLASSIFICATION:

48

49

50 (vii) PRIOR APPLICATION DATA:

51

52 (A) APPLICATION NUMBER: 60/132145

53

(B) FILING DATE: 12/9/96

54

55

56 (viii) ATTORNEY/AGENT INFORMATION:

57

58 (A) NAME: Guise, Jeffrey W.

59 (B) REGISTRATION NUMBER: 34,613

60 (C) REFERENCE/DOCKET NUMBER: 231/003

61

62

63 (ix) TELECOMMUNICATION INFORMATION:

64

65 (A) TELEPHONE: (213) 489-1600

66

(B) TELEFAX: (213) 955-0440

67

(C) TELEX: 67-3510

68

69

70 (2) INFORMATION FOR SEQ ID NO: 1:

71

72 (i) SEQUENCE CHARACTERISTICS:

73

74 (A) LENGTH: 786 base pairs

75 (B) TYPE: nucleic acid

76 (C) STRANDEDNESS: single

77 (D) TOPOLOGY: linear

78

79 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

80

ATGATCGAAA	CATAACAACCA	AACTTCTCCC	CGATCTGCGG	CCACTGGACT	GCCCATCAGC	60	
ATGAAAATTT	TTATGTATT	ACTTA	CTGTT	TTTCTTATCA	CCCAGATGAT	120	
CTTTTGCTG	TGTATCTTCA	TAGAAGGTTG	GACAAGATAG	AAGATGAAAG	GAATCTTCAT	180	
GAAGATTTG	TATTCA	TGAA	AACGATA	CAG	AGATGCAACA	240	
TTACTGA	ACT	GTGAGGAGAT	TAAAAGCCAG	TTTGAAGGCT	TTGTGAAGGA	TATAATGTTA	300
AACAAAGAGG	AGACGAAGAA	AGAAAACAGC	TTTGAAATGC	AAAAAGGTGA	TCAGAATCCT	360	
CAAATTGCGG	CACATGTCAT	AA	GTGAGGCC	AGCAGTAAA	CAACATCTGT	GTTACAGTGG	420
GCTGAAAAG	GATACTACAC	CATGAGCAAC	AACTTGGTAA	CCCTGGAAA	TGGGAAACAG	480	
CTGACCGTTA	AAAGACAA	GG	ACTCTATTAT	ATCTATGCC	AAGTCACCTT	CTGTTCCAAT	540
CGGGAAAGCTT	CGAGTC	AAAGC	TCCATT	TATA	GCCAGCCTCT	GCCTAAAGTC	600
TTCGAGAGAA	TCTTACTCAG	AGCTGCAAAT	ACCCACAGTT	CCGCCAAACC	TTGCGGGCAA	660	
CAATCCATT	ACTTGGGAGG	AGTATTGAA	TTGCAAC	AG	GTGCTTCGGT	GTTGTCAAT	720
GTGACTGATC	CAAGCCAAGT	GAGCCATGGC	ACTGGCTTCA	CGTCCTTGG	CTTACTCAA	780	
CTCTGA						786	

95

96

97

98 (2) INFORMATION FOR SEQ ID NO: 2:

99

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100 **(i) SEQUENCE CHARACTERISTICS:**

101 (A) LENGTH: 783 base pairs
 102 (B) TYPE: nucleic acid
 103 (C) STRANDEDNESS: single
 104 (D) TOPOLOGY: linear

106 **(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:**

108	ATGATAGAAA CATAACGCCA ACCTTCCCCC AGATCCGTGG CAACTGGACT TCCAGCGAGC	60
109	ATGAAGATTT TTATGTATTT ACTTACTGTGTT TTCCCTTATCA CCCAAATGAT TGGATCTGTG	120
110	CTTTTGCTG TGTATCTTC TAGAAGATTG GATAAGGTG AAGAGGAAGT AAACCTTCAT	180
111	GAAGATTTTG TATTCTAAA AAAGCTAAAG AGATGCAACA AAGGAGAAGG ATCTTTATCC	240
112	TTGCTGAAC TGTGAGGAGAT GAGAAGGCAA TTTGAAGACC TTGTCAGGAA TATAACGTTA	300
113	AACAAAGAAG AGAAAAAAAGA AACAGCTTT GAAATGCAAA GAGGTGATGA GGATCCTCAA	360
114	ATTGCAGCAC ACGTTGTAAG CGAACGCAAC AGTAATGCAAG CATCCGTTCT ACAGTGGGCC	420
115	AAGAAAGGAT ATTATACCAT GAAAAGCAAC TTGGTAATGC TTGAAAATGG GAAACAGCTG	480
116	ACGGTTAAAA GAGAAGGACT CTATTATGTC TACACTCAAG TCACCTTCTG CTCTAATCGG	540
117	GAGCCTTCGA GTCAACGCCA ATTCACTCGTC GGCCTCTGGC TGAAGCCCAAG CATTGGATCT	600
118	GAGAGAAATCT TACTCAAGGC GGCAAATACC CACAGTTCCCT CCCAGCTTTG CGAGCAGCAG	660
119	TCTGTTCACT TGGCGGAGT GTTGAATTA CAAGCTGGTG CTTCTGTGTT TGTCAACGTTG	720
120	ACTGAAGCAA GCCAAGTGAT CCACAGAGTT GGCTTCTCAT CTTTTGGCTT ACTCAAACTC	780
121	TGA	783
122		
123		
124		
125		
126		
127	(2) INFORMATION FOR SEQ ID NO: 3:	
128		
129	(i) SEQUENCE CHARACTERISTICS:	
130		
131	(A) LENGTH: 783 base pairs	
132	(B) TYPE: nucleic acid	
133	(C) STRANDEDNESS: single	
134	(D) TOPOLOGY: linear	
135		
136	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:	
137		
138	ATGATCGAAA CATAACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
139	ATGAAAATTT TTATGTATTT ACTTACTGTGTT TTTCTTATCA CCCAGATGAT TGGGTCAAGCA	120
140	CTTTTGCTG TGTATCTTC TAGAAGATTG GATAAGGTG AAGAGGAAGT AAACCTTCAT	180
141	GAAGATTTTG TATTCTAAA AAAGCTAAAG AGATGCAACA AAGGAGAAGG ATCTTTATCC	240
142	TTGCTGAAC TGTGAGGAGAT GAGAAGGCAA TTTGAAGACC TTGTCAGGAA TATAACGTTA	300
143	AACAAAGAAG AGAAAAAAAGA AACAGCTTT GAAATGCAAA GAGGTGATGA GGATCCTCAA	360
144	ATTGCAGCAC ACGTTGTAAG CGAACGCAAC AGTAATGCAAG CATCCGTTCT ACAGTGGGCC	420
145	AAGAAAGGAT ATTATACCAT GAAAAGCAAC TTGGTAATGC TTGAAAATGG GAAACAGCTG	480
146	ACGGTTAAAA GAGAAGGACT CTATTATGTC TACACTCAAG TCACCTTCTG CTCTAATCGG	540
147	GAGCCTTCGA GTCAACGCCA ATTCACTCGTC GGCCTCTGGC TGAAGCCCAAG CATTGGATCT	600
148	GAGAGAAATCT TACTCAAGGC GGCAAATACC CACAGTTCCCT CCCAGCTTTG CGAGCAGCAG	660
149	TCTGTTCACT TGGCGGAGT GTTGAATTA CAAGCTGGTG CTTCTGTGTT TGTCAACGTTG	720
150	ACTGAAGCAA GCCAAGTGAT CCACAGAGTT GGCTTCTCAT CTTTTGGCTT ACTCAAACTC	780
151	TGA	783
152		

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155	(2) INFORMATION FOR SEQ ID NO: 4:	
156		
157	(i) SEQUENCE CHARACTERISTICS:	
158		
159	(A) LENGTH: 786 base pairs	
160	(B) TYPE: nucleic acid	
161	(C) STRANDEDNESS: single	
162	(D) TOPOLOGY: linear	
163		
164	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:	
165		
166	ATGATCGAAA CATAACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
167	ATGAAAATTT TTATGTATTT ACTTACTGTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG	120
168	CTTTTGCTG TGTATCTTC TAGAAGGTTG GACAAGATAG AAGATGAAAG GAATCTTCAT	180
169	GAAGATTTG TATTCTATGAA AACGATACAG AGATGCAACA CAGGAGAAAG ATCCTTATCC	240
170	TTACTGAACT GTGAGGAGAT TAAAAGCCAG TTTGAAGGCT TTGTGAAGGA TATAATGTTA	300
171	AACAAAGAGG AGACGAAGAA AGAAAACAGC TTTGAAATGC AAAAAGGTGA TCAGAATCCT	360
172	CAAATTGCGG CACATGTCAT AAGTGAGGCC AGCAGTAAGA CAACATCTGT GTTACAGTGG	420
173	GCTGAAAAAG GATACTACAC CATGAGCAAC AACTTGGTAA CCCTGGAAAA TGGGAAACAG	480
174	CTGACCGTTA AAAGACAAGG ACTCTATTAT ATCTATGCC AAGTCACCTT CTGTTCAAT	540
175	CGGGAAAGCTT CGAGTCAAGC TCCATTATAA GCCAGCCTCT GCCTAAAGTC CCCCAGTAGA	600
176	TTCGAGAGAA TCTTACTCAG AGCTGCAAAT ACCCACAGTT CCGCCAAACCC TTGCGGGCAA	660
177	CAATCCATTC ACTTGGGAGG AGTATTTGAA TTGCAACCAG GTGCTTCGGT GTTTGTCAAT	720
178	GTGACTGATC CAAGCCAAGT GAGCCATGGC ACTGGCTTCA CGTCCTTTGG CTTACTCAAA	780
179	CTCTGA	786
180		
181		
182		
183	(2) INFORMATION FOR SEQ ID NO: 5:	
184		
185	(i) SEQUENCE CHARACTERISTICS:	
186		
187	(A) LENGTH: 783 base pairs	
188	(B) TYPE: nucleic acid	
189	(C) STRANDEDNESS: single	
190	(D) TOPOLOGY: linear	
191		
192	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:	
193		
194	ATGATCGAAA CATAACAACCA AACTTCTCCC CGATCTGCGG CCACTGGACT GCCCATCAGC	60
195	ATGAAAATTT TTATGTATTT ACTTACTGTGTT TTCCTTATCA CCCAAATGAT TGGATCTGTG	120
196	CTTTTGCTG TGTATCTTC TAGAAGATTG GATAAGGTG AAGAGGAAGT AAACCTTCAT	180
197	GAAGATTTG TATTCTAAA AAAGCTAAAG AGATGCAACA AAGGAGAAGG ATCTTATCC	240
198	TTGCTGAACT GTGAGGAGAT GAGAAGGCAA TTTGAAGACC TTGTCAAGGA TATAACGTTA	300
199	AACAAAGAAG AGAAAAAAGA AAACAGCTTT GAAATGCAA GAGGTGATGA GGATCCTCAA	360
200	ATTGCAGCAC ACGTTGTAAG CGAACGCCAAC AGTAATGCG CATCCGTTCT ACAGTGGGCC	420
201	AAGAAAGGAT ATTATACCAT GAAAAGCAAC TTGGTAATGC TTGAAAATGG GAAACAGCTG	480
202	ACGGTTAAAAA GAGAAGGACT CTATTATGTC TACACTCAAG TCACCTTCCTG CTCTAACTGG	540
203	GAGCCTTCGA GTCAACGCC ATTCACTGTC GGCCTCTGGC TGAAGCCAG CATTGGATCT	600
204	GAGAGAAATCT TACTCAAGGC GGCAAATACC CACAGTCCCT CCCAGCTTGT CGAGCAGCAG	660
205	TCTGTTCACT TGGCGGAGT GTTGAATTA CAAGCTGGTG CTTCTGTGTT TGTCAACGTC	720

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206	ACTGAAGCAA GCCAAGTGAT CCACAGAGTT GGCTTCTCAT CTTTTGGCTT ACTCAAACTC	780
207	TGA	783

208

209

210

211 (2) INFORMATION FOR SEQ ID NO: 6:

212

213 (i) SEQUENCE CHARACTERISTICS:

214

215	(A) LENGTH:	786 base pairs
216	(B) TYPE:	nucleic acid
217	(C) STRANDEDNESS:	single
218	(D) TOPOLOGY:	linear

219

220 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

221

222	ATGATAGAAA CATAACAGCCA ACCTTCCCCC AGATCCGTGG CAACTGGACT TCCAGCGAGC	60
223	ATGAAGATTT TTATGTATTT ACTTACTGTT TTTCTTATCA CCCAGATGAT TGGGTCAGCA	120
224	CTTTTGCTG TGTATCTTCA TAGAAGGTTG GACAAGATAG AAGATGAAAG GAATCTTCAT	180
225	GAAGATTTG TATTCAATGAA AACGATACAG AGATGCAACA CAGGAGAAAG ATCCTTATCC	240
226	TTACTGAAC TGTGAGGAGAT TAAAAGCCAG TTTGAAGGCT TTGTGAAGGA TATAATGTTA	300
227	AACAAAGAGG AGACGAAGAA AGAAAACAGC TTTGAAATGC AAAAAGGTGA TCAGAATCCT	360
228	CAAATTGCGG CACATGTCAT AAGTGAGGCC AGCAGTAAAA CAACATCTGT GTTACAGTGG	420
229	GCTGAAAAAG GATACTACAC CATGAGCAAC AACTTGGTAA CCCTGGAAAA TGGGAAACAG	480
230	CTGACCGTTA AAAGACAAGG ACTCTATTAT ATCTATGCC AAGTCACCTT CTGTTCCAAT	540
231	CGGGAAAGCTT CGAGTCAAAGC TCCATTATA GCCAGCCTCT GCCTAAAGTC CCCCAGTAGA	600
232	TTCGAGAGAA TCTTACTCAG AGCTGCAAAT ACCCACAGTT CCGCCAAACC TTGCGGGCAA	660
233	CAATCCATTC ACTTGGGAGG AGTATTGAA TTGCAACCAG GTGCTTCGGT GTTTGTCAAT	720
234	GTGACTGATC CAAGCCAAGT GAGCCATGGC ACTGGCTTCA CGTCCTTTGG CTTACTCAA	780
235	CTCTGA	786

236

237

238

239

240

241

242

243

244

245 (2) INFORMATION FOR SEQ ID NO: 7:

246

247 (i) SEQUENCE CHARACTERISTICS:

248

249	(A) LENGTH:	786 base pairs
250	(B) TYPE:	nucleic acid
251	(C) STRANDEDNESS:	single
252	(D) TOPOLOGY:	linear

253

254 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

255

256	ATGATAGAAA CATAACAGCCA ACCTTCCCCC AGATCCGTGG CAACTGGACT TCCAGCGAGC	60
257	ATGAAGATTT TTATGTATTT ACTTACTGTT TTTCTTATCA CCCAAATGAT TGGATCTGTG	120
258	CTTTTGCTG TGTATCTTCA TAGAAGGTTG GACAAGATAG AAGATGAAAG GAATCTTCAT	180

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